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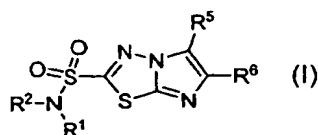
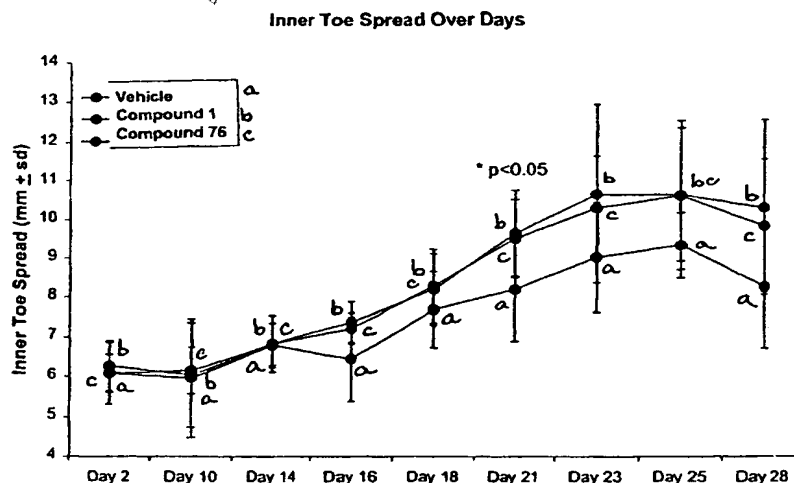
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2,364,985 14 December 2001 (14.12.2001) CA(71) Applicant (for all designated States except US): **AEGERA
THERAPEUTICS INC.** [CA/CA]; 810 Chemin du Golf,
Ile des Soeurs, Verdun, Québec H3E 1A8 (CA).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **JAQUITH, James,
B.** [CA/CA]; 59 Boise du Parc, Pincoirt, Quebec J7V 9B7
(CA). **VILLENEUVE, Gerald** [CA/CA]; 625 Rang 4,
Stoke, Quebec J0B 1H0 (CA). **BOUDREAU, Alain**
[CA/CA]; 5306 Chambond, Montreal, Quebec H2J 3N5(CA). **MORRIS, Stephen** [CA/CA]; 147 Chartwell Cres-
cent, Beaconsfield, Quebec H9W 1C2 (CA). **DURKIN,
Jon** [CA/CA]; 15 Columbus, Ottawa, Ontario K1K 1R2
(CA). **GILLARD, John, W.** [CA/CA]; 710 Westch-
ester, Baie D'Urfe, Quebec H9X 2S1 (CA). **HEWITT,
Kimberly** [CA/CA]; 307 - 263 Maclaren Street, Ottawa,
Ontario K1P 3R3 (CA). **MARSH, Nicholas, H.** [AU/CA];
5099 Jeanne-Mance, #204, Montreal, Quebec H2V 4K2
(CA).(74) Agents: **MARSMAN, Kathleen, E.** et al.; Borden Ladner
Gervais LLP, World Exchange Plaza, 100 Queen Street,
Suite 1100, Ottawa, Ontario K1P 1J9 (CA).(81) Designated States (national): AE, AG, AL, AM, AT, AU,
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(54) Title: **IMIDAZO [2,1-B]-1,3,4-THIADIAZOLE SUFLONAMIDES**

(57) Abstract: This invention relates to compounds of Formula (I) and the use of compounds of Formula (I) as neuroprotective agents in the treatment of neuronal disorders of the central and peripheral nervous systems.

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IMIDAZO [2, 1-b] -1, 3, 4-THIADIAZOLE SULFONAMIDES

FIELD OF THE INVENTION

This invention relates to sulfonamide compounds useful in the prevention of neuronal cell loss or in the treatment of nerve cell or axonal degradation.

BACKGROUND OF THE INVENTION

Various neurotrophins characterized by Neuronal Growth Factor (NGF), brain derived growth factor (BDNF), neurotrophin-3 (NT-3), and others (NT-4, CNTF, GDNF, IGF-1), have been identified as key survival factors for neurons. NGF plays a critical role in the development and maintenance of cholinergic forebrain neurons of the CNS and neurons of the peripheral nervous system (PNS); neurons of the PNS are characterized as small fiber sensory neurons associated with pain and temperature sensation, in addition to neurons of the sympathetic ganglia and dorsal root ganglia (SCGs and DRGs, respectively). BDNF plays a role in motor neuron survival. Both BDNF and NT-3 are expressed in the CNS and serve similar purposes in multiple subsets of cortical and hippocampal neurons; neurons of the CNS are characterized by those found in the brain, spinal chord, and eye. The removal of these, and related trophic factors from *in vitro* cellular media results in the degradation of the axonal processes, leading to apoptosis of cultured neurons.

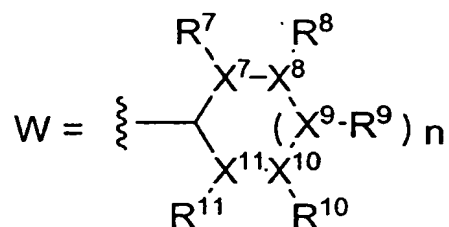
Localized tissue loss of NGF, or reduced axonal retrograde transport of NGF to the cell body, have been causally implicated in the development of peripheral neuropathies and neuropathic pain regularly observed in diabetes and HIV patients. Several double blind Phase II clinical trials have found that the systemic administration of recombinant human NGF (rhNGF) (US 5,604,202) displayed beneficial effects on neuropathic pain, physiology, and cognition related to these diseases (Apfel, S. C. *et. al. JAMA*, 248(17), 2215-2221; Apfel, S. C. *Neurology* 51, 695-702, 1998; McAurthur, J. C. *et al. Neurology* 54, 1080-1088, 2000). Side effects related to rhNGF treatment included injection site pain, hyperalgesia, and other pain related symptoms. Despite these symptoms, a large number of patients continued rhNGF treatment after unblinding.

or pharmaceutically acceptable salts thereof wherein:

R^1 and R^2 are individually selected from the group consisting of H, lower alkyl, substituted lower alkyl, and fluoroalkyl;

R^5 is selected from the group consisting of H, halogen, cyano, azide, thiocyanate, formyl, lower alkyl, substituted lower alkyl, fluoroalkyl, aralkyl, substituted aralkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

R^6 is selected from the group consisting of H, lower alkyl, substituted lower alkyl, fluoroalkyl, substituted fluoroalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, adamantly, coumarinyl, and substituted coumarinyl; or R^6 is represented by W:



wherein:

n represents 0 or 1;

the ring system containing X^7-X^{11} represents a 5 or 6 membered aromatic or heteroaromatic ring system, in which X^7-X^{11} are independently selected from the group consisting of C, N, S, and O;

when any one of X^7-X^{11} independently represents C, a respective R^7-R^{11} is independently selected from the group consisting of:

- a) H, halogen, nitro, cyano, lower alkyl, substituted lower alkyl, fluoroalkyl, aralkyl, substituted aralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, acyl, lower alkylcarbonyl, substituted lower alkylcarbonyl, arylcarbonyl, substituted arylcarbonyl, heteroarylcarbonyl, or substituted heteroarylcarbonyl;

- b) $\text{SO}_2\text{NR}^{16}\text{R}^{17}$ wherein R^{16} and R^{17} are independently selected from the group consisting of lower alkyl, substituted lower alkyl, aralkyl, substituted aralkyl, heteroaralkyl, substituted heteroaralkyl aryl, substituted aryl, heteroaryl, and substituted heteroaryl, or wherein R^{16} and R^{17} are joined to form an alkyl, substituted alkyl, heteroalkyl, or substituted heteroalkyl ring system;
- c) SO_nR^{18} wherein $n=0, 1$ or 2 , and wherein R^{18} is selected from the group consisting of lower alkyl, substituted lower alkyl, aralkyl, substituted aralkyl, heteroaralkyl, substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;
- d) XR^{19} wherein X is defined as S or O , and R^{19} is defined as alkyl, substituted alkyl, fluoroalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, acyl, lower alkylcarbonyl, substituted lower alkylcarbonyl, arylcarbonyl, substituted arylcarbonyl, heteroarylcarbonyl, substituted heteroarylcarbonyl, lower alkylaminocarbonyl, arylaminocarbonyl, or substituted arylaminocarbonyl;
- e) $\text{NR}^{14}\text{R}^{15}$ wherein R^{14} and R^{15} are defined as lower alkyl joined to form an alkyl, substituted alkyl, heteroalkyl, or substituted heteroalkyl ring system; and
- f) CO_2R^{20} wherein R^{20} is defined as H , lower alkyl, substituted lower alkyl, aralkyl, substituted aralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, or $\text{NR}^{21}\text{R}^{22}$, wherein R^{21} and R^{22} are independently selected from the group consisting of lower alkyl, aralkyl, aryl;

wherein when any one of $\text{X}^7\text{-X}^{11}$ represents N , that nitrogen is attached to the adjacent atoms by either one single and one double bond (as in pyridinyl systems), or by two single bonds (as in indolyl or imidazolyl systems);

wherein when any one of $\text{X}^7\text{-X}^{11}$ represents N , and that nitrogen is attached to the adjacent atoms by one single and one double bond, the respective $\text{R}^7\text{-R}^{11}$ represents a lone pair;

when any one of $\text{X}^1\text{-X}^5$ represents N , and that nitrogen is attached to the adjacent atoms by two single bonds (as in indolyl or imidazolyl systems), the respective $\text{R}^7\text{-R}^{11}$ is selected from the group consisting of H , lower alkyl, substituted lower alkyl, aralkyl, substituted

aralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, SO_2R^{18} , wherein R^{18} is defined as in c), COR^{18} , wherein R^{18} is defined as in c);

when $n=0$, R^7 and R^8 , or R^8 and R^9 are combined to form a fused 5,6, or 7 membered alkyl, substituted alkyl, heteroalkyl, substituted heteroalkyl, heteroaralkyl, substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, or heteroaryl ring system;

when $n=1$ and X^9 represents C, R^7 and R^8 , or R^8 and R^{10} are combined to form a fused 5, 6, or 7 membered alkyl, substituted alkyl, heteroalkyl, substituted heteroalkyl, aryl, substituted aryl, or heteroaryl ring system; and

any one of $\text{R}^7\text{-R}^{11}$ represents a lone pair when the respective $\text{X}^7\text{-X}^{11}$ represents S or O;

with the proviso that compounds 1, 4, 10, 14, 20, 60, 72, 105, 109, 111, 114, 124, 126, 127, 133, and 153 are excluded.

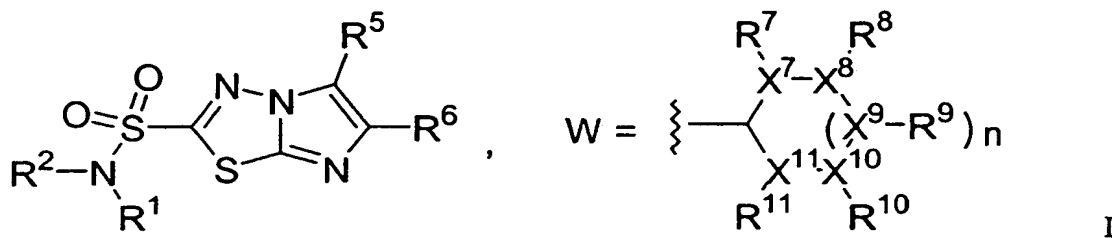
The invention relates to sulfonamide compounds of Formula I and the use of compounds of Formula I (including those noted within the proviso excluding the actual compounds themselves) for the prevention of neuronal cell loss or the treatment of nerve cell or axonal degradation, in either the central or peripheral nervous systems (CNS and PNS, respectively). The invention is useful in prevention or treatment of conditions leading to or resulting from such diseases as Alzheimer's, Huntington's, Parkinson's, muscular dystrophy, diabetes, HIV, from ischemic insults such as stroke in the brain (CNS), retinal ganglion loss following acute ocular stroke or hypertension as in glaucoma, and from infection by viruses such as Hepatitis C and Herpes Simplex. Further, the invention provides compounds for use in treatment of neuropathies resulting from chemotherapeutic agents used in the treatment of HIV and proliferative disease such as cancer, for the treatment of inflammatory diseases.

In order to identify compounds which mimic the positive effects of NGF on peripheral neurons, but which lack the inherent difficulties associated with the use of recombinant

human proteins and the rhNGF related hyperalgesia, we have developed several *in vitro* screens using a variety of neurotoxic insults. PNS neurons such as the superior cervical ganglion (SCG) and dorsal root ganglion (DRG) undergo apoptosis when subjected to NGF withdrawal. Treatment with chemotherapeutic agents such as Taxol™, cisplatin, vinblastine, vincristine, and anti-viral agents such as D4T, also induce neuronal apoptosis. Similarly, neurons of the CNS, such as cortical neurons, are sensitive to various neurotoxic agents such as β -amyloid, NMDA, osmotic shock, Taxol™ and cisplatin. Additionally, retinal ganglion neurons subjected to hypoxia undergo apoptosis.

Compounds which protect neurons from neurotoxic insults such as those mentioned above will be useful in the treatment of the peripheral neuropathies observed in diseases such as diabetes and HIV. Compounds which protect neurons from chemotherapeutic toxicity, if given concurrently with, or following, chemotherapeutic treatment will allow for the use of increasing concentrations of chemotherapeutics and/or extend the duration of chemotherapy treatments. Alternatively, enhanced recovery will be observed if such compounds are given during the recovery stages, and post treatment. These compounds will also be useful in the treatment of neurodegenerative diseases of the CNS, such as AD, PD, HD, stroke, MS, macular degeneration, glaucoma, optical stroke and retinal degeneration, and the like.

We have shown that compounds of Formula I protect SCG neurons from several neurotoxic insults, including NGF withdrawal and treatment with chemotherapeutics such as Taxol™, cisplatin, and vincristine. Compounds of Formula I also protect cortical motor neurons from malonate induced death.



When such agents are administered to mice treated with Taxol™, either during or after a two week dosing period, marked improvements are observed in the animal's general health, weight gain, and gait, as compared to animals treated with Taxol™ alone. Additionally, compounds of Formula I aid in the regeneration of neurons damaged as a result of sciatic nerve crush.

Selected examples from Formula I have been previously described. Their uses include anti-bacterial agents (Gadad, A. K. *Eur J. Med. Chem.*, 35(9), 853-857, 2000), anti-proliferative agents (Gadad, A. K. *India. Arzneim.-Forsch.*, 49(10), 858-863, 1999), and as carbonic anhydrase (CA) inhibitors (Barnish, I. T., *et. al. J. Med. Chem.*, 23(2), 117-121, 1980; Barnish, I. T. *et. al* GB 1464259, abandoned; Supuran, C, T. *Met.-Based Drugs* 2(6), 331-336, 1995 – Co(II), Cu (II), Zn(II) complexes of compound 1). Barnish *et al.* demonstrated that certain compounds reduced the number and intensity of electroshock induced seizures in rats. This anti-seizure activity was linked to increased cerebral blood flow, attributed to the ability of these compounds to inhibit CA. No direct evidence of neuronal protection as a result of these compounds has been previously demonstrated *in vitro* or *in vivo* (ie. histology, neuronal cell count, etc.).

We have found that various aryl sulfonamide CA inhibitors do not protect SCG neurons from apoptosis. These finding indicate that the neuroprotection mediated by compounds represented by Formula I is independent of their CA activity. Additionally, we have prepared several synthetic derivatives of represented by Formula I which display reduced CA inhibition inhibit CA, while retaining their neuroprotective capabilities.

The invention relates to synthetic routes for preparation of compounds represented by Formula I, and methods for the functionalization of compounds represented by Formula I.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates the protection of SCG neurons from Taxol™ induced killing provided by Compound 1 (AEG 3482).

Figure 2 illustrates the protection of cortical motor neurons from malonate killing in the presence of compound 91. 350 μ M slices of P1 rat motor cortex were treated with malonate and incubated in media for 14 days, before malonate and drug were added. Part (a) shows control motor neurons, and illustrates large diamond-shaped neurons; part (b) shows malonate treatment alone, which results in killing with a complete loss of neurons; and part (c) shows 90% rescue of cortical motor neurons in the presence of compound 91 (1 μ M) and malonate.

Figure 3 illustrates the co-treatment of HA460 and OV2008 cancer cell line with TaxolTM and Compound 1. HA460 and OV2008 cells were treated with TaxolTM and/or TaxolTM + compound 1.

Figure 4 illustrates weight loss induced by TaxolTM in Sprague Dawley rats treated with 50% HPDC vehicle (veh/veh), compound 1 dissolved in 50% HPDC at 1, 5, or 10 mg/kg (veh/1, veh/5, veh/10, respectively), or TaxolTM (9 mg/kg) + compound 1 dissolved in 50% HPDC at 1, 5, and 10 mg/kg (Tax/1, Tax/5, Tax/10) according to the dosing regime described in Example 123.

Figure 5 illustrates that gait disturbance in rats induced by TaxolTM was reduced with compound 1.

Figure 6 illustrates that compound 1 caused a reversal in H/M wave disturbance induced by TaxolTM, as indicated by H-reflex amplitude.

Figure 7 illustrates sciatic nerve recovery after crush injury, as measured by inner toe spread in male Sprague Dawley rats treated with either vehicle control; compound 1 or compound 76.

Figure 8 illustrates the effect of intravitreal compound 1, followed by subsequent daily injections on protection of DRGs after ocular stroke. Compound 1, given post stroke, protects the DRG population allowing for normal conductance.

Figure 9 illustrate the neuroprotection of cortical neurons provided by Compound 76 from amyloid beta 25-35 toxicity. Top (a) shows control untreated cultures display low level annexin V staining; middle (b) shows 48 hour treatment with amyloid beta peptide results in the appearance of apoptotic cells; and bottom (c) illustrates co-treatment with 10 uM Compound 76 prevents the occurrence of annexin V stained cells.

DETAILED DESCRIPTION

The compounds represented by Formula (I) may be referred to herein interchangeably as Compound (I). Compounds referred to herein by number (such as compound 1 or compound 76) refer to the compounds outlined as Examples 1 to 152

In the definitions of the groups of Formula I, lower alkyl means a straight-chain or branched alkyl group having 1 to 8 carbon atoms, such as methyl, ethyl, propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, pentyl, iso-amyl, neopentyl, 1-ethylpropyl, hexyl, and octyl. The lower alkyl moiety of lower alkoxy, lower alkylsulfonyl, lower alkoxycarbonyl, lower alkylaminocarbonyl has the same meaning as lower alkyl defined above. The acyl moiety of the acyl and the acyloxy group means a straight-chain or branched alkanoyl group having 1 to 6 carbon atoms, such as formyl, acetyl, propanoyl, butyryl, valeryl, pivaloyl and hexanoyl, and arylcarbonyl group described below, or a heteroarylcarbonyl group described below. The aryl moiety of the aryl, the arylcarbonyl and arylaminocarbonyl groups means a group having 6 to 16 carbon atoms such as phenyl, biphenyl, naphthyl, or pyrenyl. The heteroaryl moiety of the heteroaryl and the heteroarylcarbonyl groups contain at least one hetero atom from O, N, and S, such as pyridyl, pyrimidyl, pyrrolyl, furyl, benzofuryl, thienyl, benzothienyl, imidazolyl, triazolyl, quinolyl, iso-quinolyl, benzoimidazolyl, thiazolyl, benzothiazolyl, oxazolyl, and indolyl. The aralkyl moiety of the aralkyl and the aralkyloxy groups having 7 to 15 carbon

atoms, such as benzyl, phenethyl, benzhydryl, and naphthylmethyl. The heteroaralkyl moiety of the heteroaralkyl and the heteroaralkyloxy groups having 7 to 15 carbon such as pyridylmethyl, quinolinylmethyl, and iso-quinolinylmethyl. The substituted lower alkyl group has 1 to 3 independently-substituents, such as hydroxyl, lower alkyloxy, carboxyl, lower alkylcarbonyl, nitro, amino, mono- or di-lower alkylamino, dioxolane, dioxane, dithiolane, and dithione. The lower alkyl moiety of the substituted lower alkyl, and the lower alkyl moiety of the lower alkoxy, the lower alkoxycarbonyl, and the mono- and di-lower alkylamino in the substituents of the substituted lower alkyl group have the same meaning as lower alkyl defined above. The substituted aryl, the substituted heteroaryl, the substituted aralkyl, and the substituted heteroaralkyl groups each has 1 to 5 independently-selected substituents, such as lower alkyl, hydroxy, lower alkoxy, carboxy, lower alkoxycarbonyl, nitro, amino, mono or di-lower alkylamino, azido, and halogen. The lower alkyl moiety of the lower alkyl, the lower alkoxy, the lower alkylamino, and the mono- and di-lower alkylamino groups among the substituents has the same meaning as lower alkyl defined above. The heterocyclic group formed with a nitrogen atom includes rings such as pyrrolyl, piperidinyl, piperidino, morpholinyl, morpholino, thiomorpholino, N-methylpiperazinyl, indolyl, and isoindolyl. The cycloalkyl moiety means a cycloalkyl group of the indicated number of carbon atoms, containing one or more rings anywhere in the structure, such as cycloalkyl groups include cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclopentyl, cyclohexyl, 2-norbornyl, 1-adamantyl and the like. The fluoroalkyl moiety means a lower fluoroalkyl group in which one or more hydrogens of the corresponding lower alkyl group, as defined above, is replaced by a fluorine atom, such as CH_2F , CHF_2 , CF_3 , CH_2CF_3 , and $\text{CH}_2\text{CH}_2\text{CF}_3$.

Some of the compounds described herein contain one or more chiral centres and may thus give rise to diastereomers and optical isomers. The present invention is meant to comprehend such possible diastereomers as well as their racemic, resolved and enantiomerically pure forms, and pharmaceutically acceptable salts thereof.

The term "subject" or "patient" as used herein may refer to mammals including humans, primates, horses, cows, pigs, sheep, goats, dogs, cats and rodents.

The pharmaceutical compositions of the invention are administered to subjects in effective amounts. An effective amount means that amount necessary to delay the onset of, inhibit the progression of, halt altogether the onset or progression of or diagnose the particular condition or symptoms of the particular condition being treated. In general, an effective amount for treating a neurological disorder is that amount necessary to affect any symptom or indicator of the condition. In general, an effective amount for treating neuropathies and neuropathic pain will be that amount necessary to favorably affect mammalian cancer cell proliferation *in situ*. When administered to a subject, effective amounts will depend, of course, on the particular condition being treated; the severity of the condition; individual patient parameters including age, physical condition, size and weight; concurrent treatment; frequency of treatment; and the mode of administration. These factors are well known to those of ordinary skill in the art and can be addressed with no more than routine experimentation. It is preferred generally that a maximum dose be used, that is, the highest safe dose according to sound medical judgment.

A variety of administration routes are available. The particular mode selected will depend, of course, upon the particular condition being treated, the particular drug selected, the severity of the condition being treated and the dosage required for therapeutic efficacy. The methods of this invention, generally speaking, may be practiced using any mode of administration that is medically acceptable, meaning any mode that produces effective levels of the active compounds without causing clinically unacceptable adverse effects. Such modes of administration include oral, rectal, sublingual, topical, nasal, transdermal, intradermal or parenteral routes. The term "parenteral" includes subcutaneous, intravenous, intramuscular, or infusion. Oral routes are preferred.

Dosage may be adjusted appropriately to achieve desired drug levels, locally or systemically. Generally, daily oral doses of active compounds will be from about 0.01 mg/kg per day to 1000 mg/kg per day. It is expected that IV doses in the range of about 1 to 1000 mg/m² per day will be effective. In the event that the response in a subject is

insufficient at such doses, even higher doses (or effective higher doses by a different, more localized delivery route) may be employed to the extent that patient tolerance permits.

The compositions may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the conjugates of the invention into association with a carrier that constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing the compounds into association with a liquid carrier, a finely divided solid carrier, or both, and then, if necessary, shaping the product.

Compositions suitable for oral administration may be presented as discrete units such as capsules, cachets, tablets, or lozenges, each containing a predetermined amount of the active compound. Other compositions include suspensions in aqueous liquors or non-aqueous liquids such as a syrup, an elixir, or an emulsion.

Other delivery systems can include time-release, delayed release or sustained release delivery systems. Such systems can avoid repeated administrations of the active compounds of the invention, increasing convenience to the subject and the physician. Many types of release delivery systems are available and known to those of ordinary skill in the art. They include polymer based systems such as polylactic and polyglycolic acid, polyanhydrides and polycaprolactone; nonpolymer systems that are lipids including sterols such as cholesterol, cholesterol esters and fatty acids or neutral fats such as mono-, di and triglycerides; hydrogel release systems; silastic systems; peptide based systems; wax coatings, compressed tablets using conventional binders and excipients, partially fused implants and the like. In addition, a pump-based hardware delivery system can be used, some of which are adapted for implantation.

A long-term sustained release implant also may be used. "Long-term" release, as used herein, means that the implant is constructed and arranged to deliver therapeutic levels of the active ingredient for at least 30 days, and preferably 60 days. Long-term sustained release implants are well known to those of ordinary skill in the art and include some of

the release systems described above. Such implants can be particularly useful in treating solid tumors by placing the implant near or directly within the tumor, thereby affecting localized, high-doses of the compounds of the invention.

When administered, the Formulations of the invention are applied in pharmaceutically acceptable compositions. Such preparations may routinely contain salts, buffering agents, preservatives, compatible carriers, and optionally other therapeutic ingredients. When used in medicine the salts should be pharmaceutically acceptable, but non-pharmaceutically acceptable salts may conveniently be used to prepare pharmaceutically acceptable salts thereof and are not excluded from the scope of the invention. Such salts include, but are not limited to, those prepared from the following acids: hydrochloric, hydrobromic, sulphuric, nitric, phosphoric, maleic, acetic, salicylic, *p*-toluenesulfonic, tartaric, citric, methane sulfonic, formic, malonic, succinic, naphthalene-2-sulfonic, benzene sulfonic, and the like. Also, pharmaceutically acceptable salts can be prepared as alkaline metal or alkaline earth salts, such as sodium, potassium or calcium salts.

Suitable buffering agents include: phosphate buffers, acetic acid and a salt (1-2% W/V); citric acid and a salt (1-3% W/V); and phosphoric acid and a salt (0.8-2% W/V), as well as others known in the art.

Suitable preservatives include benzalkonium chloride (0.003-0.03% W/V); chlorobutanol (0.3-0.9% W/V); parabens (0.01-0.25% W/V) and thimerosal (0.004-0.02% W/V), as well as others known in the art.

Suitable carriers are pharmaceutically acceptable carriers. The term pharmaceutically acceptable carrier means one or more compatible solid or liquid filler, dilutants or encapsulating substances that are suitable for administration to a human or other animal. The term "carrier" denotes an organic or inorganic ingredient, natural or synthetic, with which the active ingredient is combined to facilitate the application. The components of the pharmaceutical compositions are capable of being commingled with the molecules of the present invention, and with each other, in a manner such that there is no interaction

which would substantially impair the desired pharmaceutical efficacy. Carrier Formulations suitable for oral, subcutaneous, intravenous, and intramuscular administration etc., are those which are known in the art.

The compounds of the invention may be delivered with other therapeutic agents. The invention additionally includes co-administration of compound I of the invention with other compounds known to be useful in treating neurodegenerative diseases, typified by but not limited to, acetylcholinesterase inhibitors for treating AD, such as tacrine, donepezil, and rivastigmin, and L-dopa for treating PD, and ACE inhibitors and insulin for the treatment of diabetes.

In the case of peripheral neuropathy induced by a toxic agent, compound I would be delivered separately before, simultaneously with (ie. in the form of anti-cancer cocktails, see below), or after exposure to the toxic agent. Preferably, compound I and the chemotherapeutic agent are each administered at effective time intervals, during an overlapping period of treatment in order to prevent or restore at least a portion of the neurological function destroyed by the neurotoxic or chemotherapeutic agent. The chemotherapeutic can be any chemotherapeutic agent that causes neurotoxicity, such as dideoxyinosine, deoxy cytazine, D4T, cisplatin, etoposide, vincristine, epithilone or its derivatives, or Taxol™/Taxoter™ and derivatives thereof, which are representative of the classes of agents induce neuropathies.

By “toxic agent” or “neurotixic agent” is meant a substance that through its chemical action injures, impairs, or inhibits the activity of a component of the nervous system. The list of neurotoxic agents that cause neuropathies is lengthy (see a list of candidate agents provided in Table 1). Such neurotoxic agents include, but are not limited to, neoplastic agents such as vincristine, vinblastine, cisplatin, Taxol™, or dideoxy-compounds, eg., dideoxyinosine; alcohol; metals; industrial toxins involved in occupational or environmental exposure; contaminants in food or medicinals; or over-doses of vitamins or therapeutic drugs, eg. Antibiotics such as penicillin or chloramphenicol, or mega-doses of vitamins A, D, or B6.

Table 1
Neurotoxic Agents

AGENT	ACTIVITY	AGENT	ACTIVITY
acetazolamide	diuretic	imipramine	antidepressant
acrylamide	flocculant, grouting agent	indomethacin	anti-inflammatory
adriamycin	antineoplastic	inorganic lead	toxic metal in paint, etc.
alcohol (ie. ethanol)	solvent, recreational drug	iso-niazid	antituberculosis
almitine	respiratory stimulant	lithium	antidepressant
amiodarone	antiarrhythmic	methylmercury	industrial waste
amphotericin	antimicrobial	metformin	antidiabetic
arsenic	herbicide, insecticide	methylhydrazine	synthetic intermediate
aurothioglucose	antirheumatic	metronidazole	antiprotozoal
barbiturates	anticonvulsive, sedative	misonidazole	radiosensitizer
buckthorn	toxic berry	nitrofurantoin	urinary antiseptic
carbamates	insecticide	nitrogen mustard	antineoplastic, nerve gas
carbon disulfide	industrial applications	nitous oxide	anesthetic
chloramphenicol	antibacterial	organophosphates	insecticides
chloroquine	antimalarial	ospolot	anticonvulsant
chlorethramine	antihyperlipoproteinemic	penicillin	antibacterial
cisplatin	antineoplastic	perhexiline	antiarrhythmic
clioquinol	amebicide, antibacterial	perhexiline maleate	antiarrhythmic
colestipol	antihyperlipoproteinemic	phenytoin	anticonvulsant
colchicine	gout suppressant	platin	drug component
colistin	antimicrobial	primidone	anticonvulsant
cycloserine	antibacterial	procarbazine	antineoplastic
cytarabine	antineoplastic	pyridoxine	vitamin B6
dapsone	dermatological including leprosy	sodium cyanate	antisickling
dideoxycytidine	antineoplastic	streptomycin	antimicrobial
dideoxyinosine	antineoplastic	sulphonamides	antimicrobial
dideoxythymidine	antiviral	suramin	antineoplastic
disulfiram	antialcohol	tamoxifen	antineoplastic
doxorubicin	antineoplastic	Taxol™	antineoplastic

ethambutol	antibacterial	thalidomide	antileprous
ethionamide	antibacterial	thallium	rat poison
glutethimide	sedative, hypnotic	triamterene	diuretic
gold	antirheumatic	trimethyltin	toxic metal
hexacarbons	solvents	L-tryptophan	health food additive
hormonal contraceptives		vincristine	antineoplastic
hexamethylolmelamine	fireproofing, crease proofing	vinblastine	antineoplastic
hydralazine	antihypertensive	vindesine	antineoplastic
hydroxychloroquine	antirheumatic	vitamine A or D	mega doses

Several neurotoxic agents and protocols may be used to induce apoptosis in SCG neurons. Several of these insults include the withdrawal of trophic support (for example NGF), treatment with neurotoxic chemotherapeutics such as Taxol™, cisplatin, vincristine, or vinblastine, and treatment with neurotoxic anti-virals such as D4T. Selected compounds represented by Formula I have been found to inhibit apoptosis induced by the above insults.

Neurotrophins are critical to the growth, development, and survival of small fiber neurons of the PNS. SCG neurons are neurons of the PNS that undergo apoptosis upon NGF withdrawal. In a typical experiment SCG neurons are cultured in the presence of NGF, which induces survival and neurite out-growth. After 5 days the NGF is removed by either the addition of anti-NGF polyclonal antibody (Sigma) or by repeated washings (4 times) with NGF free media, resulting in the apoptosis of up to 90% of the neurons after 48 hours, as measured by MTS staining. The addition of selected compounds of Formula I to the final cellular media provides upwards of 100% protection, at drug concentrations ranging from 3 to 50 μ M (see Example 154).

Taxol™ is regularly used in breast cancer chemotherapy. In cancer cells Taxol™ binds to the cyto-skeletal protein tubulin, thereby inhibiting normal microtubular assembly and inducing cellular apoptosis. Despite its potency as an anti-tumour agent, Taxol™ is also

toxic to neurons, inducing dose limiting peripheral neuropathies. The addition of Taxol™ (100 ng/mL) to cultured SCG neurons induces the degradation or loss of upwards of 80 % of the neurons. The addition of selected compounds of Formula I to the cellular media, concurrently with Taxol™, protects upwards of 100% of the neurons, at drug concentrations ranging from 3 to 50 μ M (see Example 155 and Figure 1).

The mechanism of Cisplatin's anti-cancer action is not fully understood, but is believed to involve DNA binding and cleavage. Cisplatin is highly toxic to neurons. The addition of cisplatin (3 μ g/mL) to cultured SCG neurons induces apoptosis of upwards of 80% of the neurons. The addition of selected compounds of Formula I to the cellular media, concurrently with cisplatin, protects upwards of 100% of the neurons, at drug concentrations ranging from 1 to 50 μ M (see Example 156).

Similarly, vincristine and vinblastine are commonly used anti-tumour agents whose mode of action involve tubulin binding. As above, the addition of vincristine (100 ng/mL) to cultured SCG neurons induces apoptosis of upwards of 80% of the neurons. The addition of selected compounds of Formula I to the cellular media, concurrently with vincristine, protects upwards of 100% of the neurons, at drug concentrations ranging from 1 to 50 μ M (see Example 157).

Various neurodegenerative diseases are related to the cellular or functional loss of motor neurons of the CNS and PNS. ALS is characterized by motor neuron loss as a result of mitochondrial dysfunction, which can be mimicked in culture by the addition of malonate to organotypic brain slices. P1 rat motor cortex brain slices were cultured for 2 weeks prior to drug and malonate addition. After an additional two weeks the slices were fixed and stained with SMI-32 antibody which selectively stains motor neurons found in layer V of the cortex. Compound 91 protected upwards of 80 % of these labeled motor neurons at a drug concentration of 1 μ M (Example 158).

Taken together, compound of Formula I display remarkable neuroprotective capabilities, against a wide range of insults in both the CNS and the PNS. One of the intended uses of

these agent is in the conjugation with chemotherapeutic agents. If compounds represented by Formula I were to protect cancer cells from the same chemotherapeutic agents, it would have limited value. Two pieces of evidence suggest these compounds do not protect cancer cells from chemotherapeutics. Selected compounds represented by Formula I have previously been shown to be anit-proliferative (Gadad, A. K. *India. Arzneim.-Forsch.*, 49(10), 858-863, 1999), suggesting these compounds will be beneficial when used in conjunction with other chemotherapeutic agents. Additionally, we have shown that compound 1 displays no protection when human ovarian carcinoma cells (OV2008) and human lung carcinoma cells (HA460) were treated with Taxol™ and/or cisplatin (see Example 159 and Figure 3).

Compound 1 and several of its derivatives have been reported to be potent inhibitors of carbonic anhydrase (CA) (Barnish, I. T., *et. al. J. Med. Chem.*, 23(2), 117-121, 1980). CA plays an important role in maintaining both intra- and extra-cellular pH levels. In an effort to determine whether the neuroprotective profile of compound 1 was due to CA inhibition, a number of well-known, cell permeable, aryl sulfonamide CA inhibitors were evaluated against the Taxol™ killing of SCGs. Dorzolamide, (Ponticello, G. S., *et. al J. Med. Chem.*, 1987, 30, 591) aminobenzolamide *N*-acetylaminobenzolamide, acetazolamide, and methazolamide (see Marten, T. H. *J. Glaucoma*, 1995, 4, 49) all failed to significantly inhibit Taxol™ induced killing of SCGs at concentrations as high as 50 μ M. Additionally, the ability of compounds represented by Formula I to inhibit CAII varied greatly depending upon the substitution patterns found on the sulfonamide or the C6 position (see Example 163). For example, compound 139 is the *N*-methyl derivative of compound 1, compound 139, displays a 100 fold decrease in CAII activity (CAII(50) 11.2 μ M and 250 nM, respectively) while retaining a similar IC(50) against Taxol (7 μ M each). Similarly, compound 77 is a poor CAII inhibitor (IC(50) 6.3 μ M), but displays a more potent against Taxol killing of SCGs (IC (50) 2 μ M). Based on these results it is clear that although compounds of Formula I are known CA inhibitors, the primary mechanism by which it is protecting neurons appears to be independent of CA inhibition.

Adenovirus overexpression of Erk1 and Erk2, two members of the MAP kinase family of signaling proteins, have been shown to stimulate neuronal out-growth and the formation of new synaptic connections in primary neurons of the PNS and CNS. Additionally, the Erks protect cultured neurons from a number of insults including neurotrophin withdrawal (Bonni, A., *et al.*, *Science*, 1999, 286, 1358-1362). A dramatic increase in Erk activity was observed in both PC12 cells and in primary cultures of sympathetic neurons when treated with compound 1. The activity of Akt, however, remained unchanged when both PC12 cells and SCGs were treated with compound 1. Akt is activated by NGF and has been demonstrated to be neuroprotective in both PNS and CNS neurons. Compound 1, therefore, protects neurons by activating a subset of NGF-stimulated signaling pathways.

Taxol™ commonly causes dose dependent peripheral neuropathies during cancer treatment. When treated with Taxol™ (9 mg/kg in Cremophor EL and ethanol) twice weekly for 3 weeks, Sprague Dawley rats displayed acute symptoms of chemotoxicity, characterized by reduced appetite, weight loss, gait disturbance (a general marker of Taxol™ induced peripheral neuropathy), and general poor health (see Example 123). For example, over a thirteen day period control animals gained an average of 50 g, whereas the Taxol™ treated animals displayed no weight gain (see Figure 2). All of the Taxol™ treated animals developed peripheral neuropathies, characterized by 'tip toe walking'. The extent of this neuropathy was analyzed by quantifying the refracted light captured by a video camera as the animals walked over a glass plate. This data was analyzed by Northern Eclipse software. The Taxol™ treated animals displayed a 46 % reduction in foot-pad contact with the glass plate, as compared to control animals (see Example 160).

When compound 1 (5 mg/kg) was given with Taxol™ (9 mg/kg) on a bi-weekly schedule, the animals displayed greatly improved health. This was characterized by normal weight gain, as compared to control (Figure 2), and a reduction in the severity of the peripheral neuropathies; a 23 % loss in foot pad contact was observed, as compared to a 46 % loss in the animals treated with Taxol™ alone (see Example 160 and Figures 4, 5 and 6). No acute signs of toxicity were observed in animals in acute toxicity studies with compound 1 alone (1, 5, and 10 mg/kg for 3 weeks).

The sciatic nerve crush model is a representative model of axonal repair and regeneration. The sciatic nerve is physically crushed with forceps at the mid-thigh; only the right leg is injured, the left leg serving as a control. The axons die from the crush point to their point of innervation. Functional loss of the axons is rapidly observed as the animals drag their right leg and the toes of the right leg no longer spread. Recovery is observed in approximately 28 days as the animals regain use of their right leg. More quantitative measurements of recovery include toe spread measurements between the digits 1 and 5 and digits 2 and 4, gait analysis and electrical conductivity from the toes to the injury site (see Example 161).

Rats were subjected to the crush injury and treated with either vehicle control or compounds 1, 76 or 111 (1 and 10 mg/kg). Functional recovery was measured as above and improved recovery was observed when the animals were treated with compound. For example, increase toe spread was observed for those animal treated with compound (see Figure 7).

Various diseases which result in loss of vision are related to increased inter-ocular pressure and ocular stroke or ischemia. Loss of the dorsal root ganglion (DRGs) occur during ischemic insult and in diseases such as diabetes and glaucoma. A model of inter-ocular ischemia involves an invasive increase in ocular pressure which results in the collapse of the central retinal artery. Retinal ischemia is confirmed by whitening of the iris and loss of red reflex. The inter-ocular pressure is normalized after 30 minutes. This procedure is performed on the right eye and the left eye serves as a control. Compound was given either by intra-vitreal injection or via SC injections at 10 mg/kg (see Example 162).

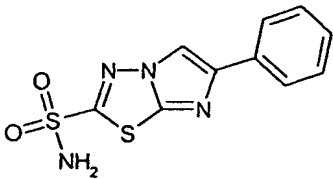
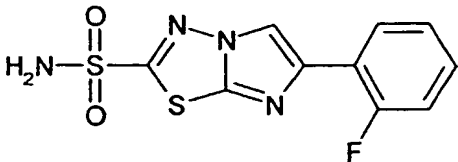
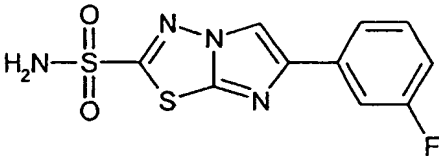
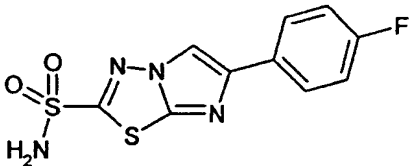
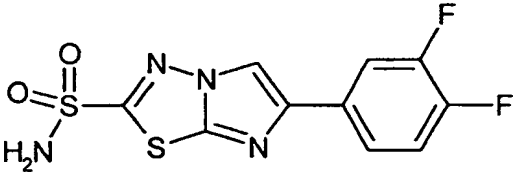
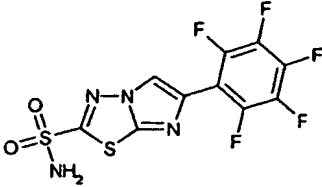
The health of the DRG neurons was assessed by means of histological staining of retinal slices and electro-retinogram (ERG) recordings. Histology of the control animals showed almost complete loss of the DRG layer, where as animals treated with compound 1 showed healthy DRG layers. Similarly, significant improvements were observed in the

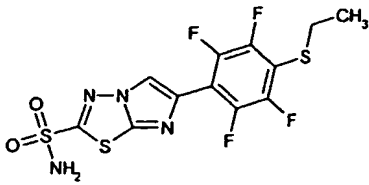
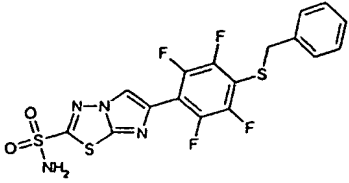
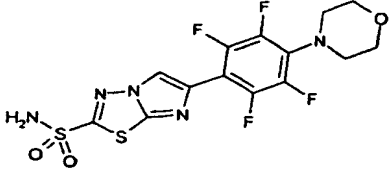
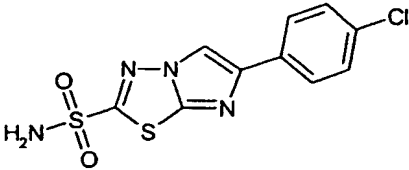
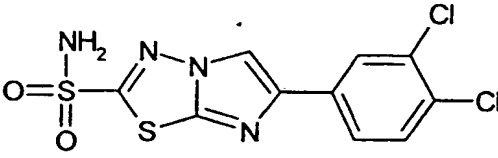
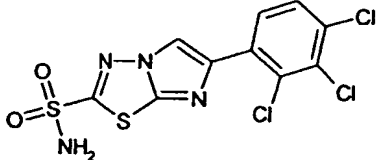
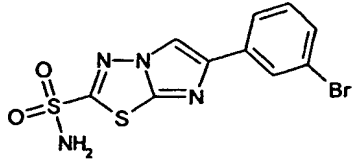
ERG for those animals treated with compound verses vehicle control animals (see Figure 8). This protection was observed for both the animals which received intra-vitreal injections and those that were treated systemically (SC).

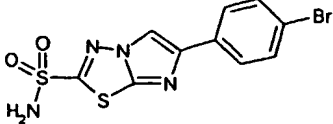
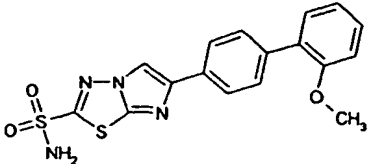
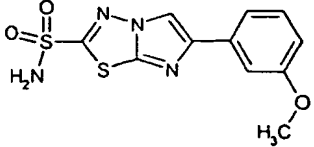
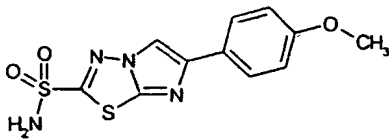
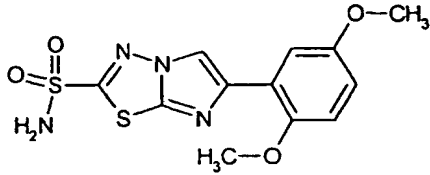
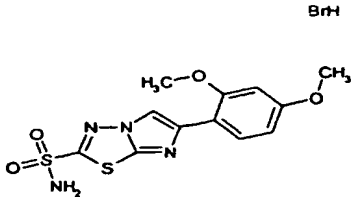
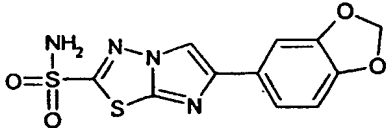
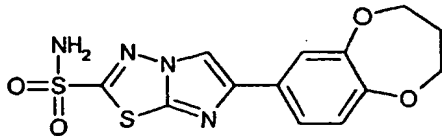
Alzheimer's disease is one of the biggest unmet medical needs in neurology. One of the main areas of AD research has been deposition and neurotoxicity of amyloid beta peptide fragments. Amyloid peptides are potently toxic to cortical neurons and protection of the cortical neurons would be a very desirable therapeutic target. We establish mixed neuronal/glial cortical cultures from postnatal rat pups. Amyloid beta peptides are potently toxic to neurons in these cultures. Exposure to 10 uM 25-35 amyloid beta increased the number of apoptotic cells compared to control. AEG33764 prevented the appearance of annexinV positive cells indicating that it protected in vitro against the amyloid beta peptide.

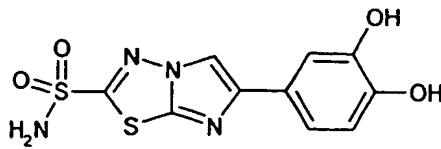
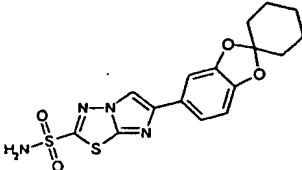
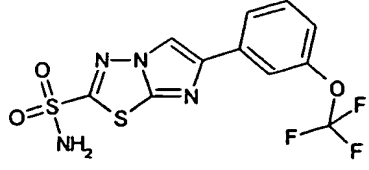
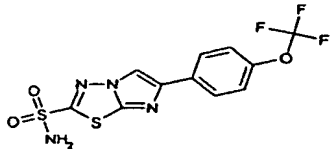
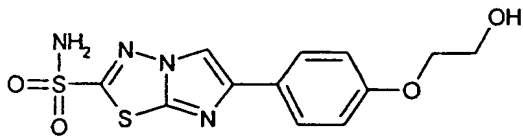
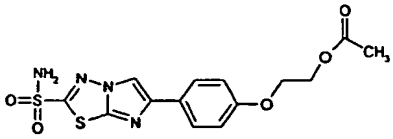
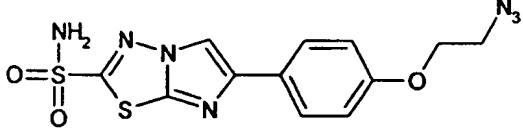
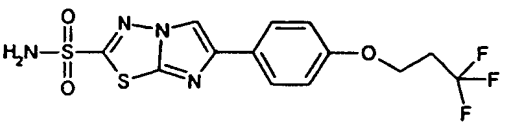
For any of the compounds having the structure of Formula I which bear similarity to those known in the art, the use of these compounds for treatment and/or prevention of neurological disorders, cancer, inflammation, or symptoms related thereto are encompassed by the invention.

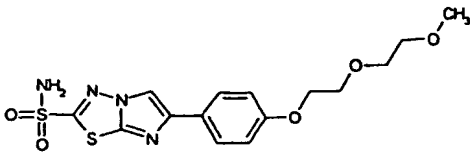
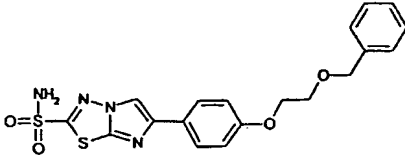
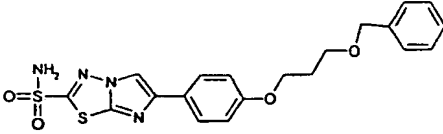
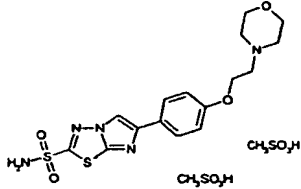
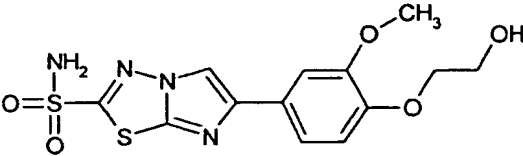
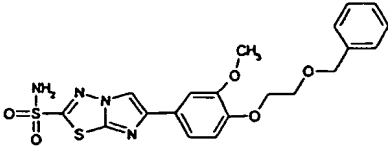
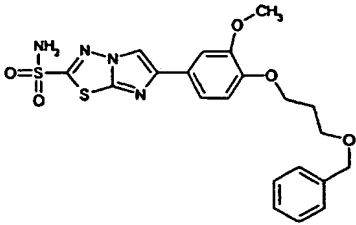
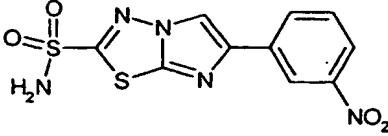
Examples of Formula I are provided below in Table 2. These compounds are referred to throughout the disclosure as their corresponding example number.

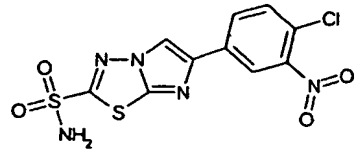
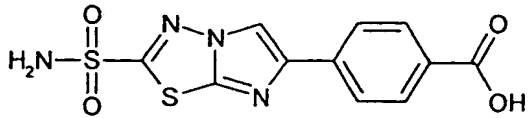
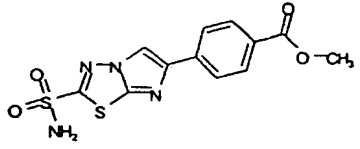
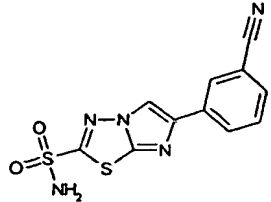
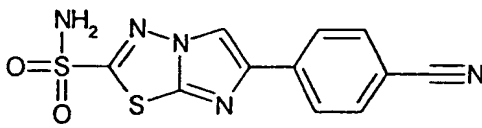
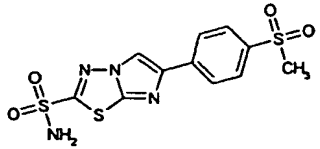
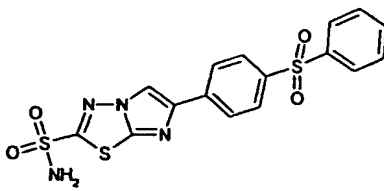
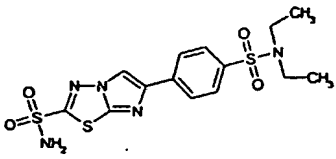
Table 2: Compounds	
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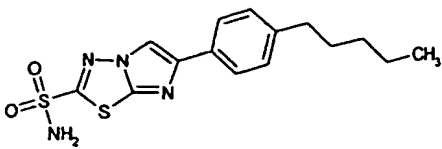
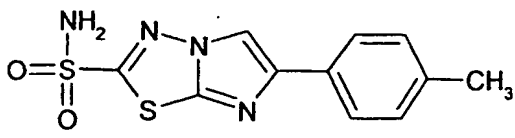
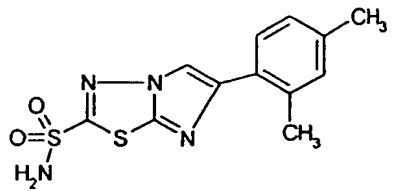
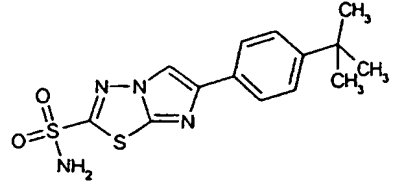
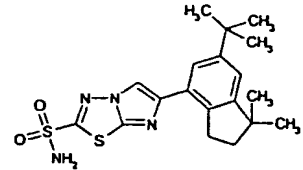
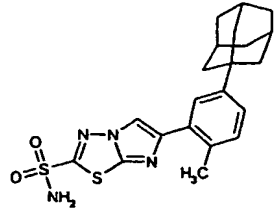
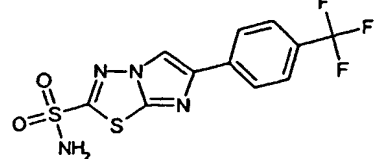
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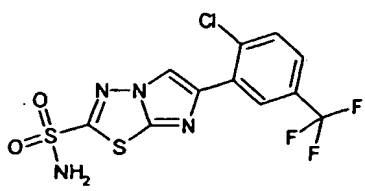
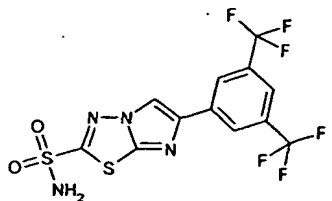
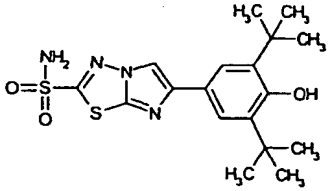
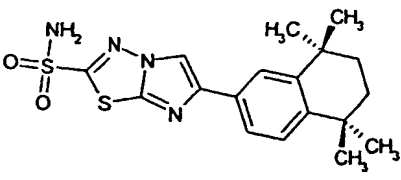
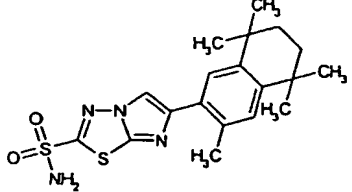
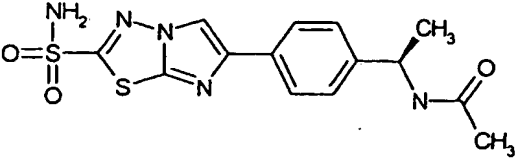
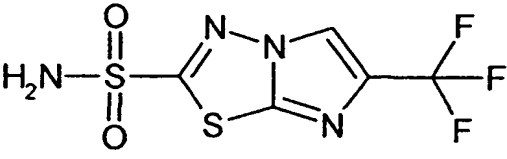
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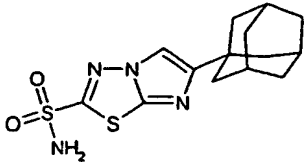
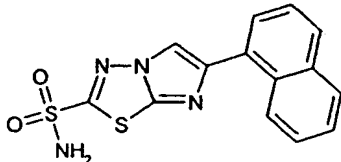
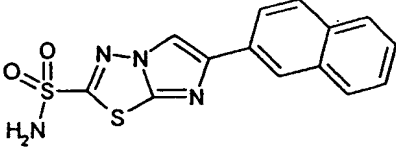
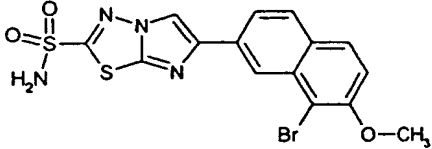
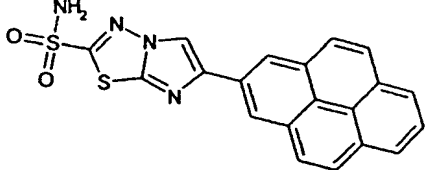
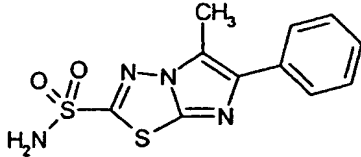
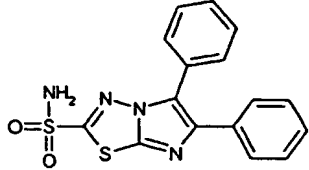
22	 <chem>N=S(=O)(=O)c1nn(Cc2cc(O)cc(O)c2)s1</chem>
23	 <chem>N=S(=O)(=O)c1nn(Cc2ccc3c(c2)OC4(CCC(C)C4)O3)s1</chem>
24	 <chem>N=S(=O)(=O)c1nn(Cc2ccc(OC(F)(F)F)cc2)s1</chem>
25	 <chem>N=S(=O)(=O)c1nn(Cc2ccc(OC(F)(F)F)cc2)s1</chem>
26	 <chem>N=S(=O)(=O)c1nn(Cc2ccc(OCCO)cc2)s1</chem>
27	 <chem>CC(=O)OCCOc1ccc(Cc2nn(Cc3s(C(=O)N)nc32)cc1</chem>
28	 <chem>N=S(=O)(=O)c1nn(Cc2ccc(OCCN=[N+]=[N-])cc2)s1</chem>
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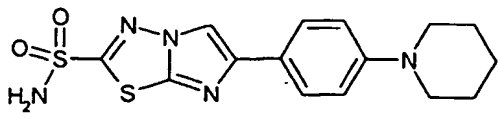
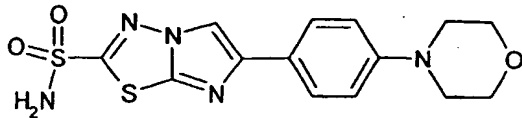
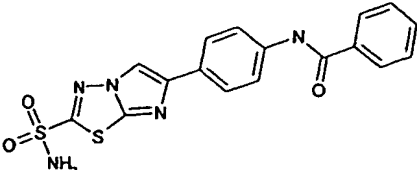
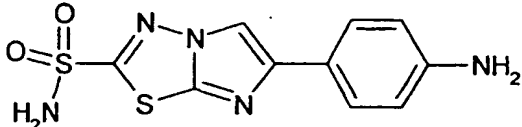
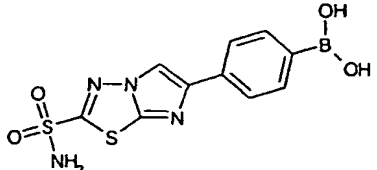
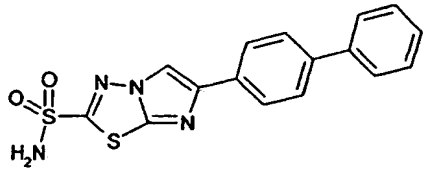
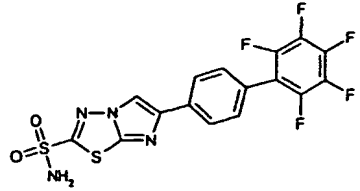
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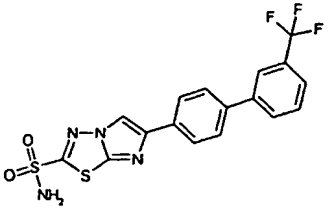
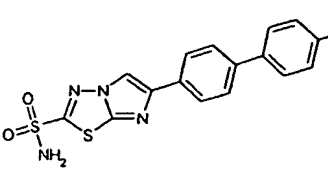
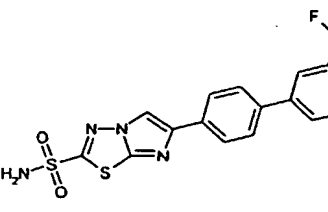
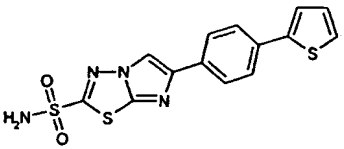
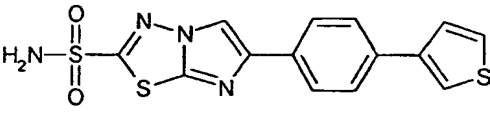
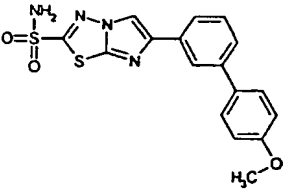
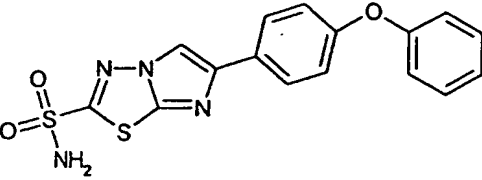
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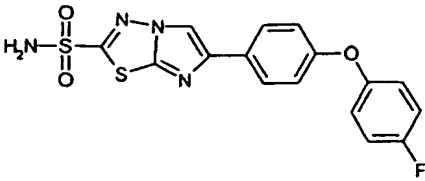
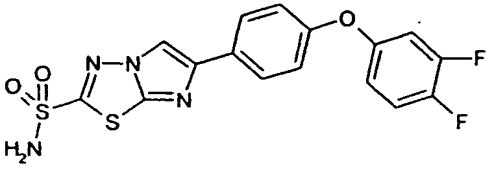
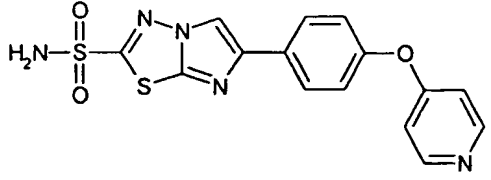
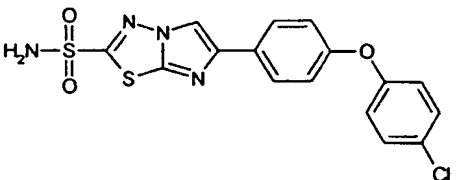
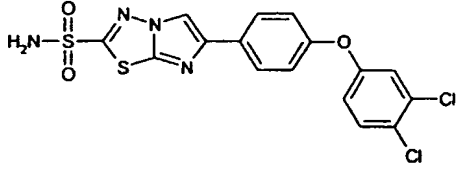
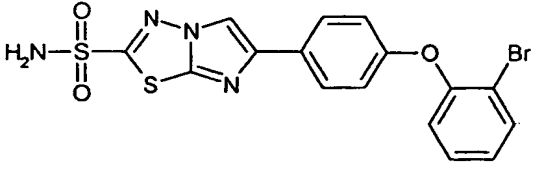
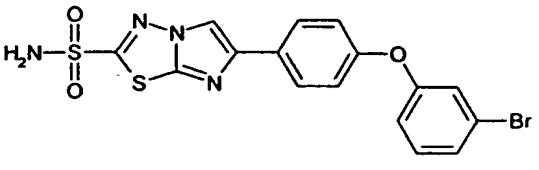
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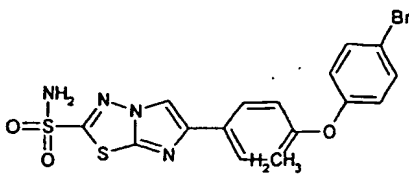
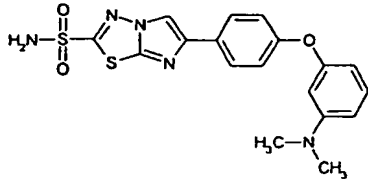
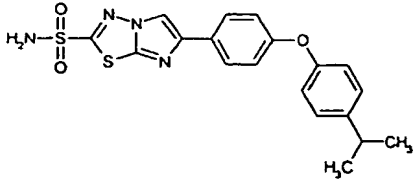
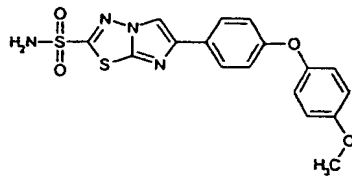
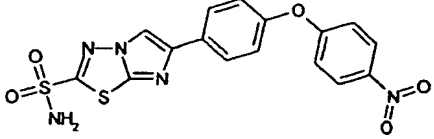
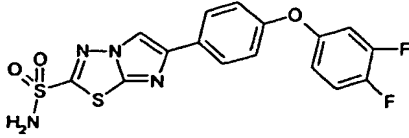
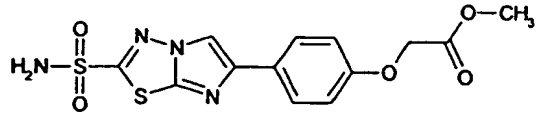
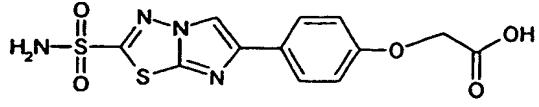
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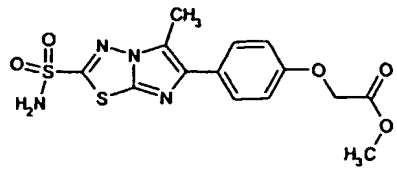
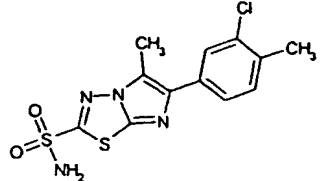
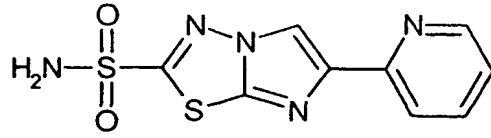
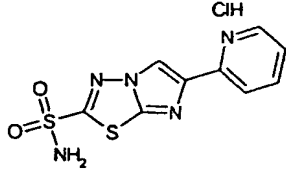
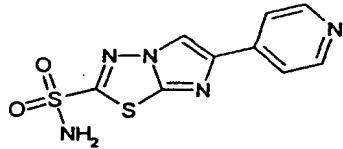
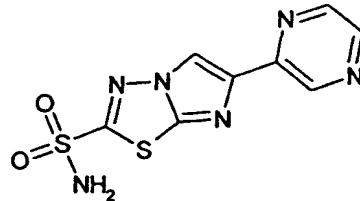
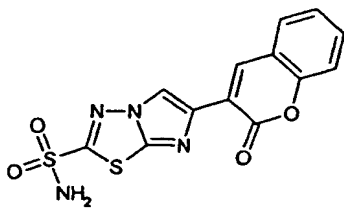
67	 <chem>NS(=O)(=O)c1nn(Cc2ccc(N3CCCCC3)cc2)s1</chem>
68	 <chem>NS(=O)(=O)c1nn(Cc2ccc(N3CCOCC3)cc2)s1</chem>
69	 <chem>NS(=O)(=O)c1nn(Cc2ccc(NC(=O)c3ccccc3)cc2)s1</chem>
70	 <chem>NS(=O)(=O)c1nn(Cc2ccc(N)cc2)s1</chem>
71	 <chem>NS(=O)(=O)c1nn(Cc2ccc(B(O)O)cc2)s1</chem>
72	 <chem>NS(=O)(=O)c1nn(Cc2ccc(cc2)-c3ccccc3)cc1s1</chem>
73	 <chem>NS(=O)(=O)c1nn(Cc2ccc(cc2)-c3cc(F)c(F)c(F)c3F)cc1s1</chem>

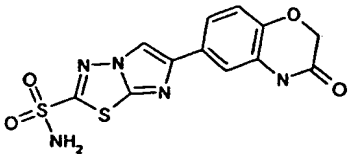
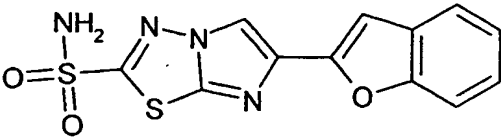
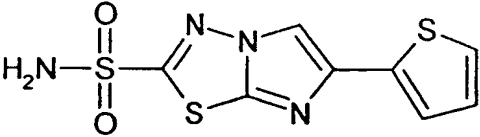
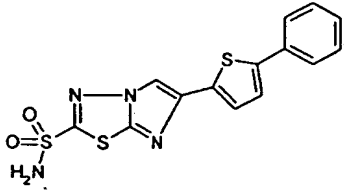
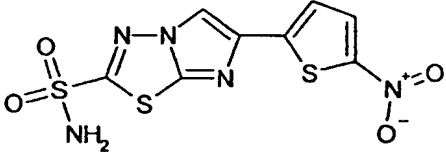
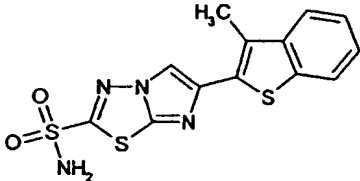
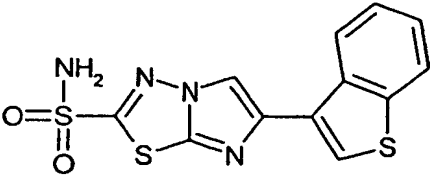
74	 <chem>NS(=O)(=O)c1nc2nc(cc12)-c3ccc(cc3)Cc4ccc(O)cc4</chem>
75	 <chem>NS(=O)(=O)c1nc2nc(cc12)-c3ccc(cc3)Cc4ccc(OC)cc4</chem>
76	 <chem>NS(=O)(=O)c1nc2nc(cc12)-c3ccc(cc3)Cc4ccccc4OC</chem>
77	 <chem>NS(=O)(=O)c1nc2nc(cc12)-c3ccc(cc3)Cc4ccc(OC)cc4</chem>
78	 <chem>NS(=O)(=O)c1nc2nc(cc12)-c3ccc(cc3)Cc4ccc(OC(F)(F)F)cc4</chem>
79	 <chem>NS(=O)(=O)c1nc2nc(cc12)-c3ccc(cc3)Cc4ccc5c(c4)OCO5</chem>
80	 <chem>NS(=O)(=O)c1nc2nc(cc12)-c3ccc(cc3)Cc4ccccc4C(F)(F)F</chem>

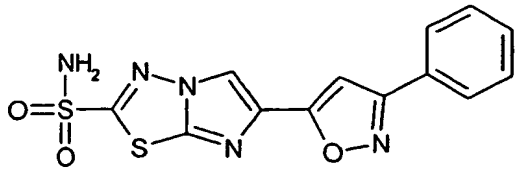
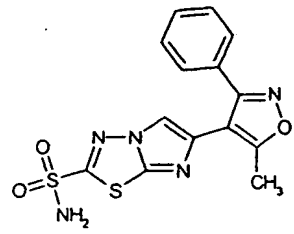
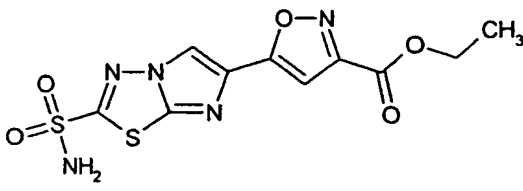
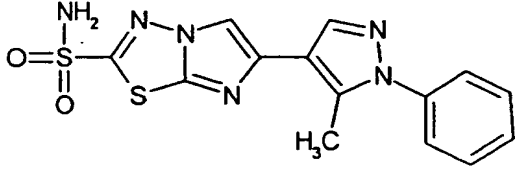
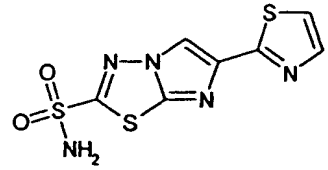
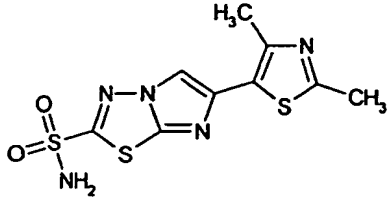
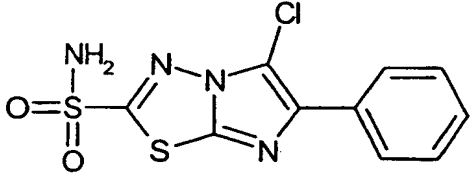
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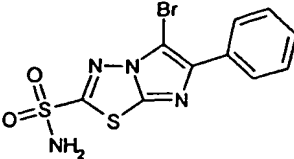
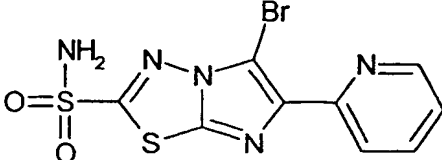
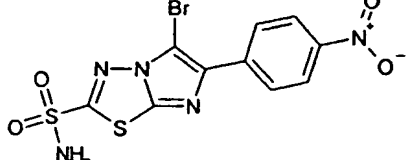
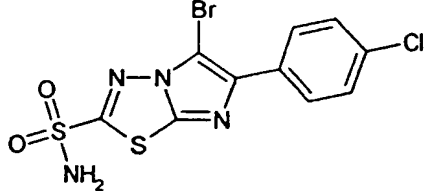
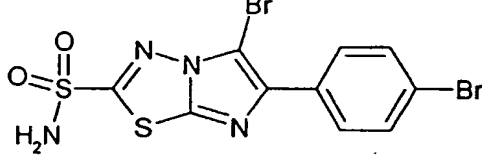
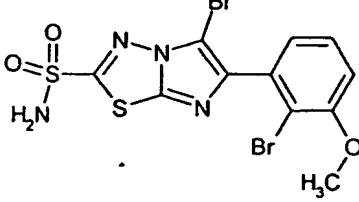
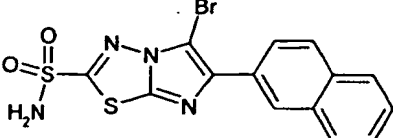
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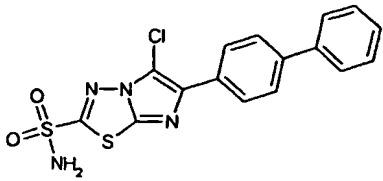
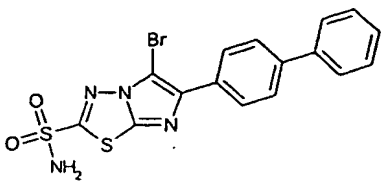
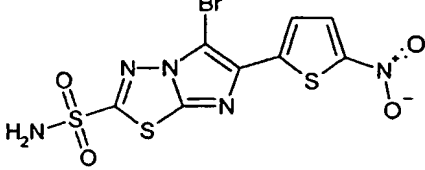
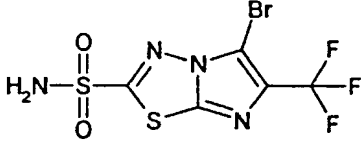
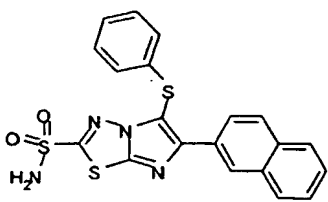
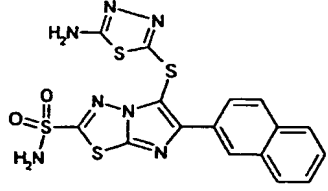
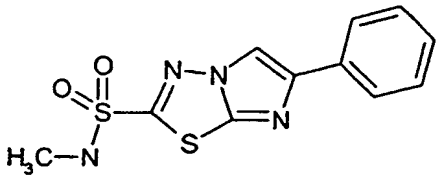
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103	 <chem>CC1=CN2C(=N1)SC(S2)S(=O)(=O)N.COC(=O)COc3ccc(cc3)-c4cc5c(nnc5s4)C</chem>
104	 <chem>CC1=CN2C(=N1)SC(S2)S(=O)(=O)N.Cc3ccc(Cl)cc3-c4cc5c(nnc5s4)C</chem>
105	 <chem>Nc1cc2c(s1)nc3ccncc3n2S(=O)(=O)Nc4ccccn4</chem>
106	 <chem>Nc1cc2c(s1)nc3cc(Cl)ccn3n2S(=O)(=O)Nc4ccccn4</chem>
107	 <chem>Nc1cc2c(s1)nc3ccncc3n2S(=O)(=O)Nc4ccncc4</chem> HBrH
108	 <chem>Nc1cc2c(s1)nc3ccncc3n2S(=O)(=O)Nc4ccncc4</chem>
109	 <chem>Nc1cc2c(s1)nc3ccncc3n2S(=O)(=O)Nc4c5ccccc5oc(=O)c4</chem>

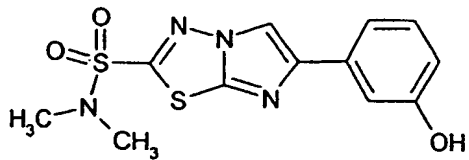
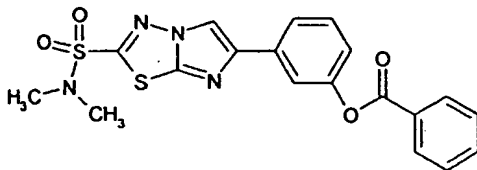
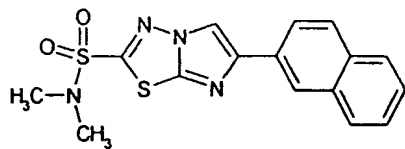
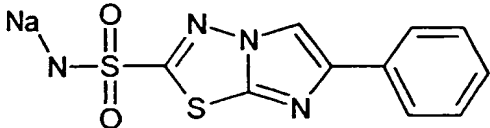
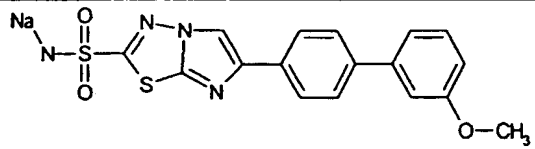
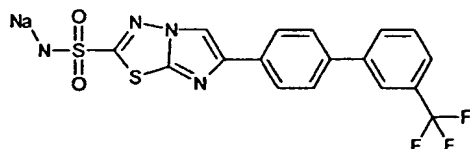
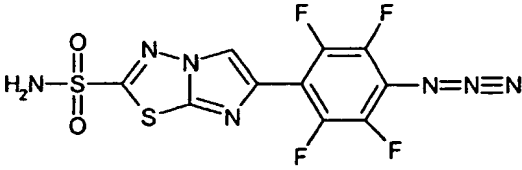
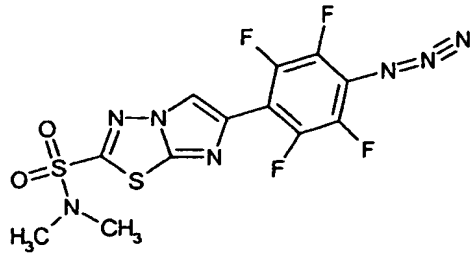
110	
111	
112	
113	
114	 BrH
115	
116	

117	 <chem>NC(=O)S(=O)(=O)c1nc2nc(cc12)-c3cc(ccc3)O=N</chem>
118	 <chem>CC1=C(C2=CC=CC=C2)ON=C1c3nc4nc(cc34)S(=O)(=O)N</chem>
119	 <chem>CCOC(=O)c1cc(ccc1O=N)-c2nc3nc(cc23)S(=O)(=O)N</chem>
120	 <chem>Cc1cc(ccn1C2=CC=CC=C2)-c3nc4nc(cc34)S(=O)(=O)N</chem>
121	 <chem>c1cc[nH]c1-c2nc3nc(cc23)S(=O)(=O)N</chem>
122	 <chem>Cc1cc(C)n(c1S)-c2nc3nc(cc23)S(=O)(=O)N</chem>
123	 <chem>Clc1nc2nc(cc12)S(=O)(=O)N-c3ccccc3</chem>

124	<p>BrH</p> 
125	
126	
127	
128	
129	
130	

131	
132	BrH 
133	
134	 BrH
135	
136	
137	

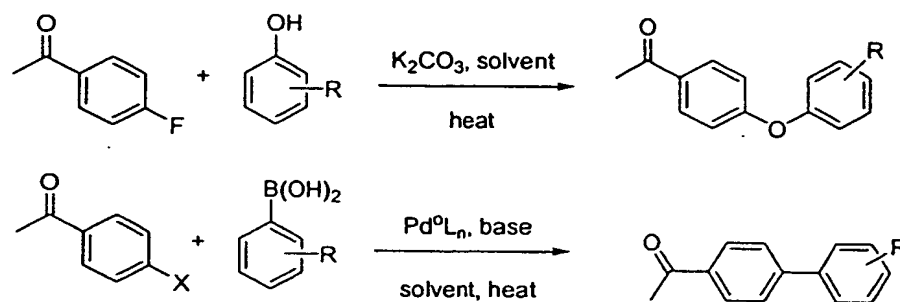
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139	 <chem>CN(C)S(=O)(=O)c1nc2nc(cc12)c3ccccc3</chem>
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141	 <chem>CCN(CC)S(=O)(=O)c1nc2nc(cc12)c3ccc(OC)cc3</chem>
142	 <chem>CCCCN(CCCC)S(=O)(=O)c1nc2nc(cc12)c3ccc(OC)cc3</chem>
143	 <chem>CN(C)S(=O)(=O)c1nc2nc(cc12)c3ccc(Br)cc3</chem>
144	 <chem>CN(C)S(=O)(=O)c1nc2nc(Br)cc2c1c3ccc(Br)cc3</chem>

145	
146	
147	
148	
149	
150	
151	
152	

SYNTHETIC PROCEDURES

2-Amino-5-thiadiazole sulfonamide, intermediate E1, was prepared by the acid hydrolysis of acetazolamide (Aldrich). Selected 2-bromoaryl ketones were purchased from either Aldrich Chemical Co. or from Maybridge Inc.

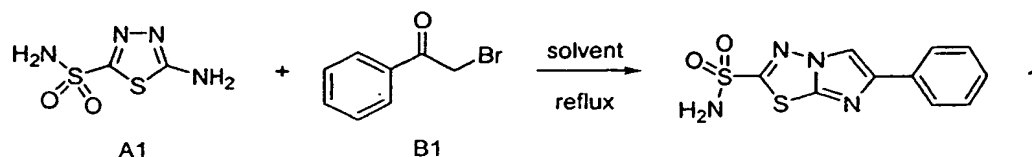
Various acetophenones were readily prepared by the following protocols. A selection of 4-phenoxyacetophenones were prepared under standard Ullmann condensation conditions by heating 4-fluoroacetophenone with the appropriate phenol and K_2CO_3 in DMF or DMAc.



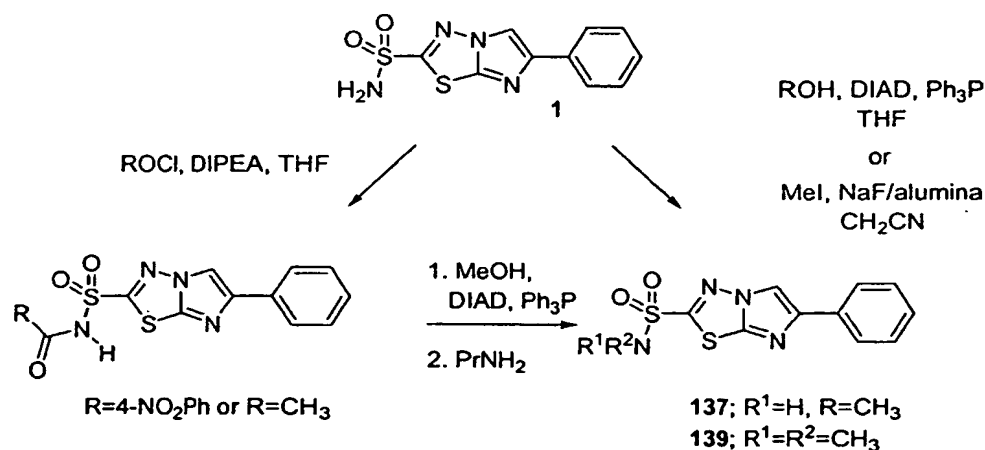
Selected 4'-arylacetophenones were prepared by Suzuki coupling of either 3'- or 4'-haloacetophenone with an arylboronic acid, or 4-acetylbenzeneboronic acid with an arylbromide, using an appropriate palladium catalyst, base, and solvent system. These products may be obtained using alternative coupling partners; ie. Suzuki coupling between aryl bromides and acetophenone boronic acids, the use of fluoborane salts, the use of Stille couplings between aryl bromides and arylstannanes, etc..

Various acetophenones were α -brominated using bromine or pyridinium tribromide in an appropriate solvent system.

The imidazo[2,1-*b*]-1,3,4-thiadiazole sulfonamides were prepared according to literature procedures. For example, compound 1 was prepared in good yield by refluxing intermediate A1, with an 2-bromoacetophenone, intermediate B1, in either alcohol or 1,4-dioxane, for 48 hours.

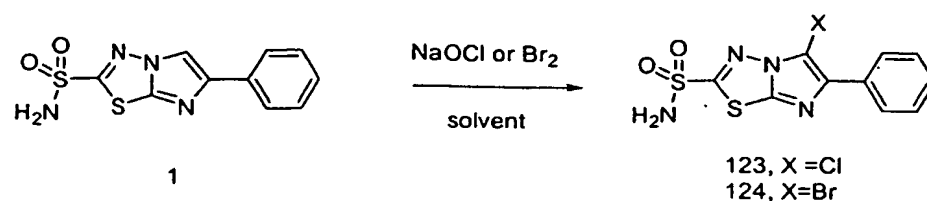


Compound 1 was either mono- or dialkylated by the treatment of compound 1 with the appropriate alcohol (1 or 2 equiv), triphenylphosphine, and DIAD or polymer supported DIAD to yield compounds such as 137 and 138. Alternatively, *N*-alkylation may be accomplished using MeI and NaF/alumina () as base, for the conversion of 1 to 137.



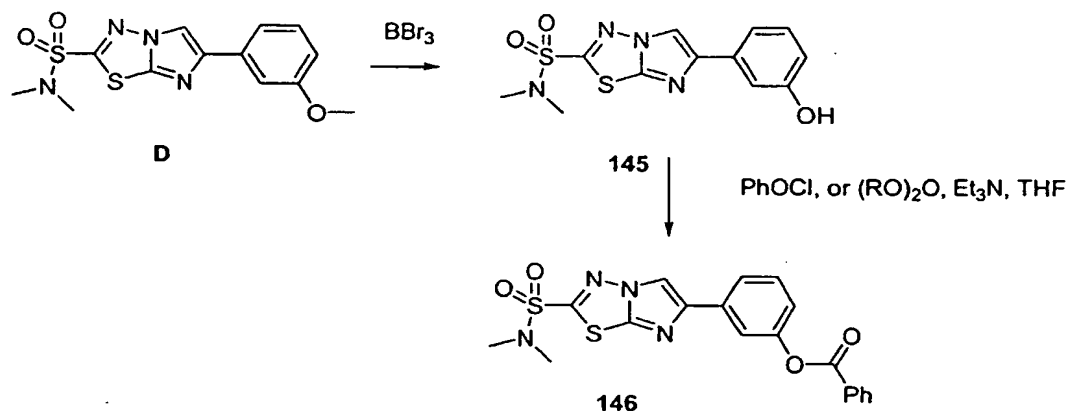
Selective mono alkylation may be accomplished by alkylation of the *N*-acyl derivatives of 1, followed by lkylation using Mitsunobu conditions, as above, followed by de-acylation with PrNH_2 , to provide the mono *N*-methyl derivative 137. This last series of reactions also works with solid supported chemistry.

Compound 1 was readily functionalized at the imidazole methine position by treatment with NaOCl or Br₂, to provide compounds 123 and 124, respectively.

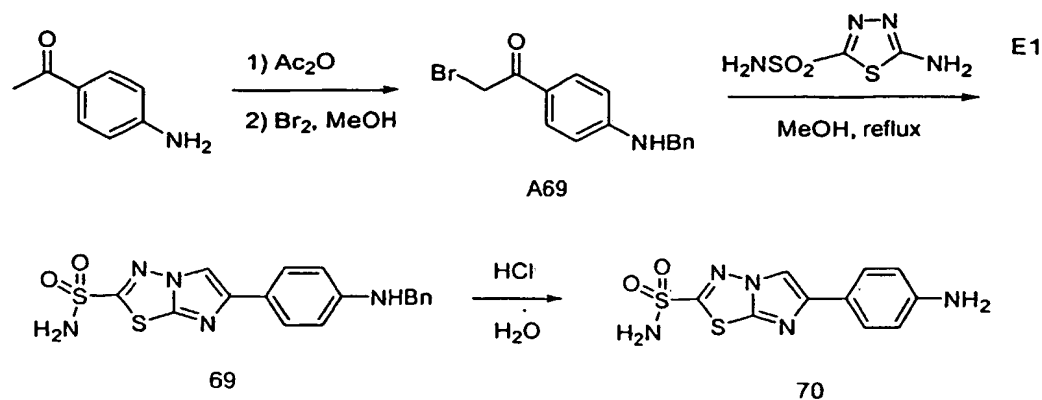


Demethylation of intermediate D with BBr_3 provides the phenolic compound 145.

Acylation of compound 145 with benzoyl chloride provides compound 146.

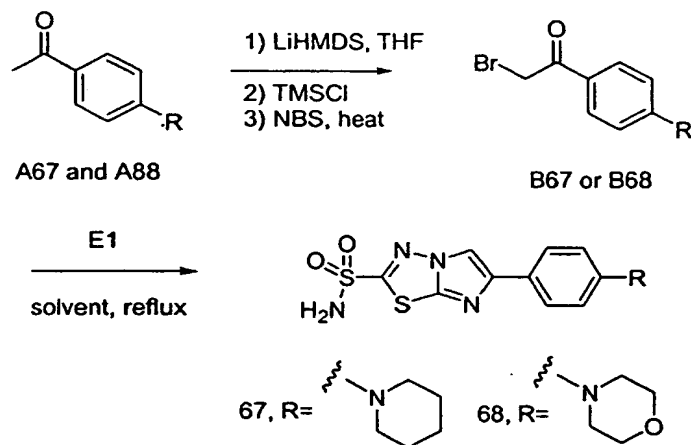


In several cases the requisite 2-bromoacetophenones were commercially available. In other cases they were prepared by the treatment of an appropriately substituted acetophenone with bromine, in an appropriate solvent, as exemplified below. Acylation of 4-aminoacetophenone was followed by bromination in MeOH to provide intermediate A69. Condensation of intermediate A69 with intermediate E1, yielded the desired compound 69.



Treatment of compound 69 with methanolic HCl provided compound 70.

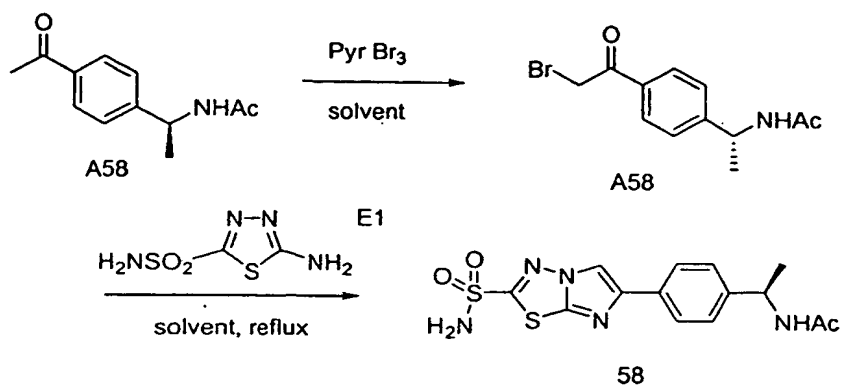
Several α -bromoketones were prepared by bromination of the appropriate enol silyl ether. Therefore, deprotonation of either 4'-piperidenylacetophenone (A67) or 4'-morpholinoacetophenone (A68) with LiHMDS, silylation with TMSCl, and quenching with *N*-bromosuccinamide, yielding the desired α -bromoketone intermediates B67 and B68, respectively, as shown below.



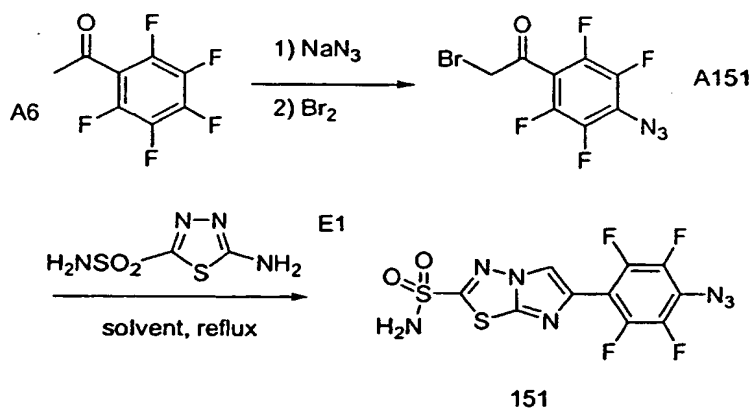
Condensation of A67 and A68 with E1, provided compounds 67 and 68, respectively.

Treatment of selected aryl ketones with bromine or pyridinium perbromide also provided the desired 2-bromoacetophenones, which were again condensed with 2-amino-1,3,4-

thiadiazole-5-sulfonamide to provide the desired 6-aryl-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamides, as shown below for compound 58.



Compound 114 was prepared using the following strategy. 2',3',4',5', 6'-Pentafluoroacetophenone, A6, was treated with sodium azide, followed by bromide, to provide 2-bromo-4'-azido-2',3',5',6'-tetrafluoroacetophenone, A151 (Keana, J. F. W.; Cai, S. X. *J. Org. Chem.*, 1990, 55, 3640).



Condensation of A151 with E1 to provided compound 151.

SELECTED COMPOUND SYNTHESIS

GENERAL PREPARATIVE METHODS

Commercially available acetophenones, 2-haloacetophenones (Intermediates A and B, respectively), phenols (Intermediate C), and benzenboronic acids (Intermediate D) were purchased from either Aldrich Chemical Company, Lancaster, Maybridge Inc, or FisherScientific. The remainder of starting materials were obtained from Aldrich Chemical Company. 2-Amino-5-thiadiazole sulfonamide, intermediate E1, was prepared by the acid hydrolysis of acetazolamide (Aldrich).

Method A: Bromination of acetophenones with bromine

The appropriate acetophenone (Intermediate A) was dissolved in diethyl ether, methylene chloride, or chloroform, and cooled to 0 °C. Bromine (1.1 equiv) was dissolved in either methylenechloride or diethyl ether and added to the solution of acetophenone via a dropping funnel. After the addition of bromine was complete 2 drops of acetic acid were added and the solution was warmed to room temperature. Solvent was removed under reduced pressure to provide crude 2-bromoacetophenone (Intermediate B) which was generally used without further purification.

Method B: Bromination of acetophenones with pyridinium tribromide

The appropriate acetophenone (Intermediate A) was dissolved in acetic acid and treated with pyridinium tribromide (1.1 equiv). The solution was stirred until all solid had reacted, the solvent was removed under reduced pressure and the residue was extracted with an appropriate solvent, washing with water. The organic layer was dried over anhydrous magnesium sulphate, filtered, and the solvent removed under reduced pressure to provide the title compounds, which was generally used without further purification.

Method C: Condensation of 2-bromoacetophenone with 2-amino-1,3,4-thiadiazole-5-sulfonamide

The appropriate 2-bromoacetophenone and 2-amino-1,3,4-thiadiazole-5-sulfonamide (1.0 equiv) were refluxed in 1,4-dioxane or an appropriate alcohol for 12-60 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 1 as a white crystalline solid. If no solid was observed the solvent was removed under reduced pressure and the title compounds were purified by silica gel chromatography, trituration, or recrystallization from an appropriate solvent.

Example 1: 6-Phenylimidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromoacetophenone (4.00 g, 20.0 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (3.60 g, 20.0 mmol) were refluxed in ethanol (150 mL) for 60 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 1 as a white crystalline solid (2.50 g, 44 %). ¹H NMR (200MHz, DMSO-*d*⁶) δ 8.89 (s, 1H), 8.72 (br s, 2H), 7.90 (d, 2H), 7.43 (t, 2H), 7.32 (t, 1H).

Example 2: 6-(2-Fluorophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 2 was prepared by the bromination of 2'-fluoroacetophenone with bromine, according to Method A, followed by condensation with 2-amino-1,3,4-thiadiazole-5-sulfonamide hydrochloride, according to Method C, to provide a white solid. ¹H NMR (200 MHz, DMSO-*d*⁶) δ 8.75 (br s, 2H), 8.6 (d, 1 H, *j*=3.6 Hz), 8.1 (m, 1H), 7.3 (m, 3H).

Example 3: 6-(3-Fluorophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 3 was prepared by the bromination of 3'-fluoroacetophenone with bromine, according to Method A, followed by condensation with 2-amino-1,3,4-thiadiazole-5-sulfonamide hydrochloride, according to Method C, to provide a white solid. ¹H NMR (200 MHz, DMSO-*d*⁶) δ 8.95 (s, 1H), 8.74 (s, 1 H), 7.73 (m, 2H), 7.5 (m, 1H), 7.1 (m, 1H).

Example 4: 6-(4-Fluorophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-4'-fluoroacetophenone (1.08 g, 5.0 mmol) 2-amino-1,3,4-thiadiazole-5-sulfonamide hydrochloride (900 mg, 5.0 mmol) were refluxed in ethanol (25 mL) for 48 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected

by filtration to provide compound 19 as a white crystalline solid (17 mg). ^1H NMR (200MHz, DMSO- d_6) δ 8.87 (s, 1H), 8.74 (br s, 2H), 7.40 (m, 2H), 7.28 (m, 2H).

Example 5: 6-(3,4-Difluorophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide 2-Chloro-3',4'-difluoroacetophenone (190 mg, 1.0 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (150 mg, 1.0 mmol), and CETAB (437 mg, 1.20 mmol) were refluxed in dioxane (5 mL) for 48 hrs. The solvent was removed under reduced pressure and the resulting solid was purified by silica gel chromatography, eluting with 1:1 hexane/ethyl acetate, to provide compound 20 (173 mg, 57%) as a white crystalline solid. ^1H NMR (200MHz, acetone- d_6) δ 8.41 (d, 1H), 8.26 (m, 1H), 7.92 (br s, 2H), 7.24-7.08 (m, 2H).

Example 6: 6-(2,3,4,5,6-Pentafluorophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-1-(pentafluorophenyl)ethan-1-one (2.89 g, 10.0 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (1.80 g, 10.0 mmol) were refluxed in ethanol (20 mL) for 60 hrs. Solvent was evaporated and the crude solid was purified by flash chromatography using 20 : 80 : 0.1 ethyl acetate : hexanes : acetic acid to provide compound 115 as white needles (125 mg, 3.4 %). ^1H NMR (200MHz, DMSO- d_6) δ 8.82 (s, 1H), 8.78 (s, 2H).

Example 7: 6-(4-Ethylthio-2,3,5,6-tetrafluorophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2',3',4',5',6'-Pentafluoroacetophenone (2.5 mmol) was heated with ethanethiol (2.5 mmol) in THF (5 mL). Solvent was removed under reduced pressure to provide the desired compounds as a white solid. Pyridinium tribromide (920 mg, 2.5 mmol) was added and the mixture stirred for 16 hours. Solvent was removed under reduced pressure and 2-amino-1,3,4-thiadiazole-5-sulfonamide (450 mg, 2.5 mmol) was added and solution was refluxed for 48 hours. The solution was cooled to room temperature and filtered to provide compound 7 as a white solid (173 mg, 17%). ^1H NMR (200 MHz, DMSO- d_6) δ 8.82 (s, 1H), 8.79 (br s, 2H), 3.00 (quart, $J=8.2\text{Hz}$, 2H), 1.98 (t, $J=8.2\text{Hz}$, 3H).

Example 8: 6-(4-Benzylthio-2,3,5,6-tetrafluorophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 8 was prepared according to the procedure described for compound 7, using benzylmercaptan in the place of ethanethiol, to provide compound 8 as a white solid (204 mg, 16%). ¹H NMR (200 MHz, DMSO-*d*⁶) δ 8.83 (s, 1H), 8.79 (br s, 2H), 7.23 (s, 5H), 4.21 (s, 2H).

Example 9: 6-(4-Morpholino-2,3,5,6-tetrafluorophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 6 (100 mg) was dissolved in 1 ml of DMSO and 1ml of morpholine was added, the solution was heated to 90 °C for 2 hrs. The solution was allowed to cool down to room temperature and ethyl acetate was added. The solution was washed twice with water and once with brine. The organic layer was separated dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by silica gel chromatography using a 20% to 50% ethyl acetate in hexanes gradient to give a white solid (30 mg). ¹H NMR (200 MHz, CDCl₃) δ 8.05 (s, 1H), 3.76 (m, 4 H), 3.27 (m 4 H).

Example 10: 6-(4-Chlorophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide
Compound 21 was obtained from Talon.

Example 11: 6-(3,4-Dichlorophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide
2-Bromo-3',4'-dichloroacetophenone (267 mg, 1.0 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide hydrochloride (180 mg, 1.00 mmol) were refluxed in ethanol (20 mL) for 48 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 11 as a white crystalline solid (91 mg, 26 %). ¹H NMR (200MHz, DMSO-*d*⁶) δ 9.01 (s, 1H), 8.74 (s, 2H), 8.13 (d, 1H), 7.89 (dd, 1H), 7.70 (d, 1H).

Example 12: 6-(2,3,4-trichlorophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide
Compound 12 was prepared by bromination of 2',3',4'-trichloroacetophenone with bromine according to Method A, and condensation of the corresponding 2-

bromoacetophenone with 2-amino-1,3,4-thiadiazole-5-sulfonamide, according to Method C, to yield compound 12 as a white solid (22% yield). ¹H NMR (200MHz, DMSO-d⁶) δ 9.00 (s, 1H), 8.74 (br s, 2H), 8.07 (d, J=8.5Hz, 2H), 7.74 (d, J=8.5Hz, 2H).

Example 13: 6-(3-bromophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide
Compound 13 was prepared by bromination of 3'-bromoacetophenone with bromine according to Method A, and condensation of the corresponding 2-bromoacetophenone with 2-amino-1,3,4-thiadiazole-5-sulfonamide, according to Method C, to yield compound 13 as a white solid. ¹H NMR (200MHz, DMSO-d⁶) δ 8.94 (d, J=1.3Hz, 1H), 8.74 (br s, 2H), 8.08 (d, J=1.1Hz, 1H), 7.90 (dd, J=1.4, 7.7Hz, 1H), 7.48 (d, J=7.7Hz, 1H), 7.38 (t, J=8.6Hz, 1H).

Example 14: 6-(4-Bromophenyl)-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide
2-Bromo-4'-bromoacetophenone (2.78 g, 10.0 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (1.80 g, 12.0 mmol) were refluxed in 1,4-dioxane (25 mL) for 16 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 24 as a white crystalline solid (3.60 g). ¹H NMR (200MHz, DMSO-d⁶) δ 8.92 (s, 1H), 8.75 (br s, 2H), 7.85 (d, 2H), 7.62 (d, 2H).

Example 15: 6-(2-Methoxyphenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide
2-Bromo-2'-methoxyacetophenone (916 mg, 4.0 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (720 mg, 4.0 mmol) were refluxed in ethanol (20 mL) for 48 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 40 as a white crystalline solid. ¹H NMR (200MHz, DMSO-d⁶) δ 9.68 (br s, 1H), 8.78 (br s, 2H), 8.12 (d, 1H), 7.34 (t, 1H), 7.11 (d, 1H), 7.05 (t, 1H), 3.96 (s, 3H).

Example 16: 6-(3-Methoxyphenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide
2-Bromo-3'-methoxyacetophenone (1.00 g, 4.37 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (786 mg, 4.37 mmol) were refluxed in 1,4-dioxane (25 mL) for 48 hrs. The

resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 41 as a white crystalline solid (375 mg, 28 %).

^1H NMR (200MHz, DMSO- d_6) δ 8.89 (s, 1H), 8.73 (br s, 2H), 7.46 (s, 2H), 7.33 (t, $J=8.1\text{Hz}$, 1H), 6.88 (d, $J=7.3\text{Hz}$, 1H), 3.80 (s, 3H). ^{13}C NMR (50MHz, DMSO- d_6) δ 164.3, 159.8, 146.7, 145.2, 134.8, 130.0, 117.4, 113.7, 111.4, 110.3, 55.1.

Example 17: 6-(4-Methoxyphenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide
2-Bromo-4'-methoxyacetophenone (2.29 g, 10.0 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (1.80 g, 12.0 mmol) were refluxed in 1,4-dioxane (25 mL) for 24 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 42 as a white crystalline solid (2.65 g, 86 %). ^1H NMR (200MHz, DMSO- d_6) δ 8.83 (s, 1H), 8.00 (d, 2H), 7.13 (d, 2H), 3.88 (s, 3H).

Example 18: 6-(2,5-Dimethoxyphenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-2',5'-dimethoxyacetophenone (261 mg, 1.00 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (180 mg, 1.20 mmol) were refluxed in 1,4-dioxane (7 mL) for 48 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 44 as a white crystalline solid (15.5 mg, 5 %). ^1H NMR (200MHz, DMSO- d_6) δ 8.72 (br s, 2H), 8.60 (s, 1H), 7.70 (d, 1H), 7.04 (d, 1H), 6.87 (dd, 1H), 3.89 (s, 3H), 3.74 (s, 3H).

Example 19: 6-(2,4-Dimethoxyphenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide
2-Bromo-2',4'-dimethoxyacetophenone (259 mg, 1 mmol) and 2-amino-1,3,4-thiadiazole-2-sulfonamide (180 mg, 1 mmol) were refluxed in ethanol for 5 days. After cooling the resulting precipitate was filtered and washed with methanol, providing 43 (56 mg) as a beige powder. ^1H NMR (200MHz, DMSO- d_6) δ 8.69 (br s, 2H), 8.47 (s, 1H), 8.06 (d, $J=8.8\text{ Hz}$, 1H), 6.66 (s, 1H), 6.62 (d, $J=2.4\text{ Hz}$, 1H), 3.93 (s, 3H), 3.80 (s, 3H).

Example 20: 6-(1,3-Benzodioxol-5-yl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

1-(1,3-benzodioxol-5-yl)-2-bromoethan-1-one (100 mg, 0.41 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (74 mg, 0.41 mmol) were refluxed in ethanol (5 mL) for 30 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 95 as a pale yellow powder (40 mg, 44 %). ¹H NMR (200MHz, DMSO-d⁶) δ 8.75 (s, 1H), 8.69 (s, 2H), 7.43 (m, 2H), 6.97 (d, J = 8.6 Hz, 1H), 6.04 (s, 2H).

Example 21: 6-(3,4-dihydro-2H-1,5-benzodioxepin-7-yl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-1-(3,4-dihydro-2H-1,5-benzodioxepin-7-yl)ethan-1-one (542 mg, 2 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (360 mg, 2 mmol) were refluxed in ethanol (10ml) for 60 hours. The resulting mixture was cooled on ice and the resulting precipitate collected by suction filtration, giving 96 (310 mg) as a yellow powder. ¹H NMR (200MHz, DMSO-d⁶) δ 8.79 (s, 1H), 8.71 (br s, 2H), 7.49 (s, 1H), 7.45 (d, J=7.9Hz, 1H), 7.00 (d, J=7.9Hz, 1H), 4.2-4.0 (m, 4H), 2.10 (t, J=4.9Hz, 2H). ¹³C NMR (50MHz, DMSO-d⁶) δ 163.9, 151.4, 151.0, 146.2, 145.1, 128.9, 122.0, 120.1, 118.2, 110.7, 70.6, 31.5.

Example 22: 6-(3,4-Dihydroxyphenyl-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide 2-Chloro-3',4'-dihydroxyacetophenone (186 mg, 1.0 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (150 mg, 1.0 mmol), and CETAB (10 mg) were refluxed in dioxane (5 mL) for 48 hrs. The solvent was removed under reduced pressure and the resulting solid was purified by silica gel chromatography, eluting with 1:1 hexane/ethyl acetate, to provide compound 48 (11 mg, 4%) as a white crystalline solid. ¹H NMR (200MHz, acetone-d⁶) δ 8.38 (s, 1H), 8.10 (br s, 2H), 7.84 (br s, 2H), 7.44 (d, 1H), 7.39 (dd, 1H), 6.88 (d, 1H).

Example 23:

Compound 23 was prepared by the bromination of 2'-fluoroacetophenone with bromine, according to Method A, followed by condensation with 2-amino-1,3,4-thiadiazole-5-sulfonamide hydrochloride, according to Method C, to provide a white solid. ¹H NMR (200 MHz, DMSO-d⁶) δ 8.75 (br s, 2H), 8.6 (d, 1 H, j=3.6 Hz), 8.1 (m, 1H), 7.3 (m, 3H).

Example 24: 6-(3-trifluoromethoxyphenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 24 was prepared by bromination of 3'-trifluoromethoxyacetophenone with bromine according to Method A, and condensation of the corresponding 2-bromoacetophenone with 2-amino-1,3,4-thiadiazole-5-sulfonamide, according to Method C, to yield compound 24 as a white solid (22% yield). ¹H NMR (200MHz, DMSO-d⁶) δ 9.01 (s, 1H), 8.74 (br s, 2H), 7.92 (d, J=7.6Hz, 1H), 7.91 (s, 1H), 7.57 (t, J=7.6Hz, 1H), 7.30 (d, J=7.6Hz, 1H).

Example 25: 6-(4-trifluoromethoxyphenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 25 was prepared by bromination of 4'-trifluoromethoxyacetophenone with bromine according to Method A, and condensation of the corresponding 2-bromoacetophenone with 2-amino-1,3,4-thiadiazole-5-sulfonamide, according to Method C, to yield compound 25 as a white solid (22% yield). ¹H NMR (200MHz, DMSO-d⁶) δ 8.93 (s, 1H), 8.73 (s, 2H), 8.00 (d, J=8.8Hz, 2H), 7.43 (d, J=8.4Hz, 2H).

Example 26

Compound 26 was prepared in a manner similar to compound 31.

¹H NMR (200 MHz, DMSO-d⁶) δ = 3.71 (t, 2H, J = 4.6 Hz), 4.00 (t, 2H, J = 4.9 Hz), 6.99 (d, 2H, J = 8.3 Hz), 7.81 (d, 2H, J = 8.2 Hz), 8.67 (s, 2H), 8.73 (s, 1H)

Example 27

Step 1: Compound 26 (472 mg, 1.39 mmol), di-*tert*-butyldicarbonate (383 μL, 1.67 mmol), triethylamine (194 μL, 1.39 mmol), DMAP (20 mg, 0.16 mmol) were added to DMF (5 mL) and stirred at RT under N₂ for 45 min. The volatiles were removed under reduced pressure and the contents washed with H₂O and EtOAc. The organic layer was collected, dried over MgSO₄. ¹H NMR (200MHz, CDCl₃) δ 1.23 (s, 9H), 3.73 (t, 2H, J = 5.4 Hz), 4.00 (t, 2H, J = 5.6 Hz), 7.02 (d, 2H, J = 8.8 Hz), 7.82 (d, 2H, J = 8.4 Hz), 8.69 (s, 1H).

Step 2 : The material from step 1 (627 mg, 1.39 mmol), acetic anhydride (158 μ L, 1.67 mmol), triethylamine (233 μ L, 1.67 mmol), DMAP (21 mg, 0.17 mmol) were added to DMF (5 mL) and stirred under N₂ for 3 h. The volatiles were removed under reduced pressure and the contents washed with H₂O and EtOAc. The organic layer was collected, dried over MgSO₄. ¹H NMR (200MHz, CDCl₃) δ 1.20 (s, 9H), 2.08 (s, 3H), 4.09 (b, 2H), 4.40 (b, 2H), 6.90 (d, 2H, J = 8.8 Hz), 7.62 (d, 2H, J = 8.4 Hz).

Step 3 : The material from Step 3 was dissolved in 10 mL TFA/CH₂Cl₂ (1:1) and stirred for 30 min at RT. The volatiles were removed under reduced pressure and the contents washed with NaHCO₃ (aq) and EtOAc. The organic layer was collected, dried over MgSO₄. The product was recrystallized from ethanol. ¹H NMR (200MHz, DMSO-d₆) δ 2.03 (s, 3H), 4.20 (b, 2H), 4.31 (b, 2H), 7.02 (d, 2H, J = 8.8 Hz), 7.82 (d, 2H, J = 8.4 Hz), 8.69 (s, 2H), 8.76 (s, 1H).

Example 28 :

Step 1 : 2-Bromoethanol, K₂CO₃ and 4-hydroxy acetophenone were refluxed together in MeOH. The solvent was removed under reduced pressure and the residue treated to standard ethyl acetate/water work-up to provide a white semi-solid. ¹H NMR (200 MHz, CDCl₃) δ 2.55 (s, 3H), 3.65 (t, 2H, J = 6.1 Hz), 4.35, t, 2H, J = 6.4 Hz), 6.94 (d, 2H, J = 9.5 Hz), 7.93 (d, 2H, J = 8.8 Hz).

Step 2 : The material from Step 1 (50 mg, 0.216 mmol), NaN₃ (20 mg, 0.307 mmol) were dissolved in acetone (5 mL) and H₂O (0.5 mL) and heated to reflux with stirring for 16 h. Solvent was removed and the desired compounds was obtained in quantitative yield. ¹H NMR (200 MHz, CDCl₃) δ 2.55 (s, 3H), 3.63 (t, 2H, J = 4.6 Hz), 4.21 (t, 2H, J = 5.19 Hz), 6.95 (d, 2H, J = 8.85 Hz), 7.94 (d, 2H, J = 8.9 Hz).

Step 3 : The material from Step 2 was brominated according to Method A and purified on silica gel (4:1, CH₂Cl₂:Hexanes) to give 2-Bromo-4'-(2-azidoethoxy)acetophenone. ¹H NMR (200 MHz, CDCl₃) δ 3.63 (t, 2H, J = 4.9 Hz), 4.21 (t, 2H, J = 5.2 Hz), 4.40 (s, 2H), 6.95 (d, 2H, J = 9.2 Hz), 7.94 (d, 2H, J = 8.6 Hz).

Step 4 : 2-Bromo-4'-(2-azidoethoxy)acetophenone was condensed with 1,3,4-thiadiazole-2-sulfonamide according to Method C yielding an off yellow solid. ¹H NMR (200 MHz,

DMSO-d⁶) δ 3.65 (t, 2H, J = 4.0 Hz), 4.20 (t, 2H, J = 4.3 Hz), 7.02 (d, 2H, J = 8.2 Hz), 7.83 (d, 2H, J = 8.2 Hz), 8.71 (s, 2H), 8.76 (s, 1H).

Example 29 :

Step 1 : 3-Bromo-1,1,1-trifluoropropane, K₂CO₃ and 4'-hydroxyacetophenone were refluxed together in MeOH for 16 hours. Volatiles were removed under reduced pressure and the residue subjected to standard ethyl acetate/water work-up. ¹H NMR (200 MHz, CDCl₃) δ 2.48-2.70 (m, 5H), 4.19 (t, 2H, J = 6.4 Hz), 6.87 (d, 2H, J = 8.8 Hz), 7.87 (d, 2H, 9.2 Hz).

Step 2: 4'-(3,3,3-trifluoropropoxy)acetophenone was brominated according to Method A. ¹H NMR (200 MHz, CDCl₃) δ 2.48-2.70 (m, 2H), 4.27 (t, 2H, J = 6.4 Hz), 4.40 (2, 2H) 6.96 (d, 2H, J = 8.8 Hz), 7.98 (d, 2H, 9.2 Hz).

Step 3: 2-Bromo-4'-(3,3,3-trifluoropropoxy)acetophenone was condensed with 1,3,4-thiadiazole-2-sulfonamide according to Method C, yielding an off yellow solid. ¹H NMR (200 MHz, DMSO-d⁶) δ 2.65-2.85 (m, 2H), 4.23 (t, 2H, J = 6.2 Hz), 7.02 (d, 2H, J = 8.6 Hz), 7.83 (d, 2H, J = 8.6 Hz), 8.71 (s, 2H), 8.76 (s, 1H).

Example 30 :

Step 1 : 1-Bromo-2-(2-methoxyethoxy)ethane, K₂CO₃ and 4'-hydroxyacetophenone were refluxed together in MeOH for 16 hours. Volatiles were removed under reduced pressure and the residue subjected to standard ethyl acetate/water work-up. ¹H NMR (200 MHz, CDCl₃) δ 2.55(s, 3H) 3.39 (s, 3H), 3.56 (t, 2H, J = 4.0 Hz), 3.71 (t, 2H, J = 4.6 Hz), 3.88 (t, 2H, 4.3 Hz), 4.21 (t, 2H, J = 4.9 Hz), 6.94 (d, 2H, J = 8.8. Hz), 7.92 (d, 2H, J = 8.2 Hz).

Step 2 : The material from Step 1 was brominated according to Method A. ¹H NMR (200 MHz, CDCl₃) δ 3.40 (s, 3H), 3.56 (t, 2H, J = 4.0 Hz), 3.71 (t, 2H, J = 4.6 Hz), 3.88 (t, 2H, 4.3 Hz), 4.21 (t, 2H, J = 4.9 Hz), 4.40 (s, 2H), 6.94 (d, 2H, J = 8.8. Hz), 7.92 (d, 2H, J = 8.2 Hz).

Step 3: The Material from Step 2 was condensed with 2-amino-1,3,4-thiadiazole-2-sulfonamide according to Method C to provide a yellow solid. ¹H NMR (200 MHz,

DMSO-d⁶) δ 3.23 (s, 3H), 3.47 (b, 2H), 3.57 (b, 2H), 3.73 (b, 2H), 4.11 (b, 2H), 7.00 (d, 2H, J = 8.2 Hz), 7.81 (d, 2H, J = 8.6 Hz), 8.70 (s, 2H), 8.74 (s, 1H).

Example 31:

Step 1: 4-Hydroxyacetophenone (500 mg, 3.67 mmol), K₂CO₃ (510 mg, 3.69 mmol) and benzyl-2-bromoethyl ether (580 μ L, 3.67 mmol) were suspended in ethanol (25 mL). The mixture was heated to reflux with stirring for 21 h. The volatiles were removed under reduced pressure and the contents washed with H₂O and EtOAc. The organic layer was collected, dried over MgSO₄ and purified on silica gel (1:3 EtOAc/Hexanes) yielding 4'-(2-Benzyloxyethoxy)acetophenone as a white crystalline solid (600 mg, 61%). ¹H NMR (200 MHz, CDCl₃) δ 2.55 (s, 3H), 3.85 (t, 2H, J = 4.9 Hz), 4.21 (t, 2H, J = 4.9 Hz), 4.64 (s, 2H), 6.95 (d, 2H, J = 8.9 Hz), 7.35 (b, 5H), 7.93 (d, 2H, J = 8.8 Hz).

Step 2: 4-(2-Benzyloxyethoxy)acetophenone (447 mg, 1.65 mmol) was brominated using Method A to yield a yellow oil (51% conversion). ¹H NMR (200 MHz, CDCl₃) δ 3.85 (t, 2H, J = 4.9 Hz), 4.21 (t, 2H, J = 4.9 Hz), 4.64 (s, 2H), 4.80 (s, 2H), 6.95 (d, 2H, J = 8.9 Hz), 7.35 (b, 5H), 7.93 (d, 2H, J = 8.8 Hz).

Step 3: 6-(4'-(2-Benzyloxyethoxy)phenyl)-imidazo[2,1-b]-1,3,4-thiadiazole-2 sulfonamide
The crude material from Step 2 (299 mg, 0.86 mmol) was condensed with 2-amino-1,3,4-thiadiazole-2-sulfonamide using Method C in 2-propanol, yielding a yellow solid (140 mg, 38%). ¹H NMR (200 MHz, DMSO-d⁶) δ 3.77 (b, 2H), 4.18 (b, 2H), 4.55 (s, 2H), 7.01 (d, 2H, J = 8.5 Hz), 7.33 (b, 5H) 7.81 (d, 2H, J = 8.5 Hz), 8.69 (s, 2H), 8.74 (s, 1H).

Example 32 :

Step 1: 4-Hydroxyacetophenone (500 mg, 3.67 mmol), K₂CO₃ (510 mg, 3.69 mmol) and benzyl-3-bromopropyl ether (547 μ L, 3.67 mmol) were suspended in ethanol (25 mL). The mixture was heated to reflux with stirring for 21 h. The volatiles were removed under reduced pressure and the contents washed with H₂O and EtOAc. The organic layer was collected, dried over MgSO₄ and purified on silica gel (1:3 EtOAc/Hex) yielding 4'-(2-Benzyloxyethoxy)acetophenone as a white crystalline solid (737 mg, 71%). ¹H NMR (200 MHz, CDCl₃) δ 2.08-2.14 (m, 2H), 2.56 (s, 3H), 3.67 (t, 2H, J = 6.1 Hz), 4.16 (t, 2H, J = 6.1 Hz), 4.53 (s, 2H), 6.92 (d, 2H, J = 8.5 Hz), 7.31 (s, 5H), 7.93 (d, 2H, J = 8.9 Hz).

Step 2: 4'-(3-Benzyloxy)propoxyacetophenone (447 mg, 1.65 mmol) was brominated using Method A to provide a yellow oil (82 % conversion). ^1H NMR (200 MHz, CDCl_3) δ 2.08-2.14 (m, 2H), 3.67 (t, 2H, $J = 6.1$ Hz), 4.16 (t, 2H, $J = 6.1$ Hz), 4.40 (s, 2H), 4.53 (s, 2H), 6.92 (d, 2H, $J = 8.5$ Hz), 7.93 (d, 2H, $J = 8.9$ Hz)

Step 3: The crude material from step 3 (671 mg, 1.85 mmol) was condensed with 2-amino-1,3,4-thiadiazole-2-sulfonamide using Method C (2-propanol) provided a yellow solid (85 mg, 10 %). ^1H NMR (200 MHz, DMSO-d_6) δ 1.96-2.06 (m, 2H), 3.58 (t, 2H, $J = 6.4$ Hz), 4.08 (t, 2H, $J = 5.8$ Hz), 4.47 (s, 2H), 6.98 (d, 2H, $J = 8.5$ Hz), 7.30 (s, 2H), 7.80 (d, 2H, $J = 8.5$ Hz), 8.69 (s, 2H), 8.73 (s, 1H).

Example 33: 6-(4-(2-Morpholinoethoxy)phenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide bis(methanesulfonic acid)

6-(4-(2-Morpholinoethoxy)phenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide was prepared according to Method C. ^1H NMR (200 MHz, DMSO-d_6) δ 8.70 (s, 1H), 7.82 (8.2Hz, 2H), 7.05 (d, $J=8.2\text{Hz}$, 2H), 4.34 (m, 4H), 3.81 (m, 4H), 3.48 (m, 2H), 3.26 (m, 2H).

6-(4-(2-Morpholinoethoxy)phenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide (100 mg) was suspended in MeOH (2 mL) and treated with methanesulfonic acid (100 μL). Diethyl ether (10 mL) was added and the resulting solid was filtered and washed with diethyl ether to provide compound 33. ^1H NMR (200 MHz, D_2O) δ 8.09, 7.53 (d, $J=6.7\text{Hz}$, 2H), 6.97 (d, $J=6.7\text{Hz}$, 2H), 4.43 (s, 2H), 4.20 (m, 2H), 3.96 (br t, 2H), 3.70 (m, 4H), 3.35 (m, 2H), 2.80 (br s, 4H).

Example 34:

Compound 34 was prepared in a manner similar to that described for compound 32.

^1H NMR (200 MHz, DMSO-d_6) δ 3.71 (t, 2H, $J = 4.9$ Hz), 3.82 (s, 2H), 3.98 (t, 2H, $J = 4.6$ Hz), 7.01 (d, 1H, $J = 8.2$ Hz), 7.40-7.48 (m, 3H), 8.71 (s, 2H), 8.79 (s, 1H).

Example 35:

Compound 35 was prepared in a manner similar to compound 32.

^1H NMR (200 MHz, DMSO- d^6) δ 8.78 (s, 1H), 8.67 (s, 2H), 7.48 (s, 1H), 7.40 (d, $J=8.6\text{Hz}$, 1H), 7.34 (s, 5H), 7.02 (d, $J=8.6\text{Hz}$, 1H), 4.56 (s, 2H), 4.14 (br s, 2H), 3.83 (s, 3H), 3.77 (br s, 2H).

Example 36:

Compound 36 was prepared in a manner similar to compound 32.

^1H NMR (200 MHz, DMSO- d^6) δ 8.78 (s, 1H), 8.70 (s, 2H), 7.47 (s, 1H), 7.42 (d, $J=8.2\text{Hz}$, 1H), 7.30 (s, 5H), 7.01 (d, $J=8.2\text{Hz}$, 1H), 4.47 (s, 2H), 4.06 (t, $J=6.1\text{Hz}$, 2H), 3.80 (s, 3H), 3.59 (t, $J=6.3\text{Hz}$, 2H), 1.99 (t, $J=6.1\text{Hz}$, 2H).

Example 37: 6-(3-Nitrophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide
2-Bromo-3'-nitroacetophenone (224 mg, 1.0 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (180 mg, 1.20 mmol) were refluxed in 1,4-dioxane (7 mL) for 48 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 37 as a yellow crystalline solid (54 mg, 15 %). ^1H NMR (200MHz, DMSO- d^6) δ 9.12 (s, 1H), 8.75 (br s, 2H), 8.70 (t, 1H), 8.31 (d, 1H), 8.14 (d, 1H), 7.72 (t, 1H).

Example 38: 6-(3-nitro-4-chlorophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 38 was prepared by bromination of 3-nitro-4-chloroacetophenone with bromine according to Method A, and condensation of the corresponding 2-bromoacetophenone with 2-amino-1,3,4-thiadiazole-5-sulfonamide, according to Method C, to yield compound 38 as a white solid (22% yield). ^1H NMR (200MHz, DMSO- d^6) δ 9.09 (s, 1H), 8.77 (s, 2H), 8.53 (s, 1H), 8.18 (d, $J=6.9\text{Hz}$, 2H), 7.86 (d, $J=8.5\text{Hz}$, 2H).

Example 39:

Step1: 4-Acetylbenzoic acid (1.00 g, 6.09 mmol) was suspended in methanol (10mL). Hydrochloric acid (500 μL) was added. The reaction mixture was refluxed overnight. The resulting suspension was cooled to -10°C , filtered and the solid washed with cold methanol (3 x 2 mL) to provide methyl 4-acetylbenzoate as a white solid (799

mg, 74%). ^1H NMR (200MHz, CDCl_3) δ 8.12 (d, $J = 8.9\text{Hz}$, 2H), 8.01 (d, $J = 8.9\text{Hz}$, 2H), 3.95 (s, 3H), 2.65 (s, 3H).

Step2 Methyl 4-acetylbenzoate (200 mg, 1.12 mmol) was suspended in chloroform (5mL) and treated with pyridinium tribromide (359 mg, 1.12mmol). The reaction mixture was stirred overnight. One half equivalent of pyridinium tribromide (179 mg, 0.56 mmol) was added to the reaction mixture and stirred for two days. The solvent was removed under reduced pressure. Standard aqueous/ethyl acetate workup provided a brown solid, which was identified as a 8:12:3 mixture of starting material, methyl 4-(2-bromoacetyl)benzoate and methyl 4-(2,2-dibromoacetyl)benzoate compound. ^1H NMR (200MHz, DMSO-d^6) δ 8.08 (d, $J = 6.7\text{Hz}$, 4H), 4.98 (s, 2H), 3.87 (s, 3H).

Step 3 Methyl 4-(2-bromoacetyl)benzoate (100 mg, 0.39 mmol) and 5-amino-1,3,4-thiadiazole-2-sulfonamide (70mg, 0.39 mmol) were refluxed together in methanol (10 mL) for 48 hours. The resulting suspension was cooled to -10°C , filtered and the solid washed with cold methanol (3 x 2 mL) to provide compound 39 as a white solid (12.9 mg, 9.35%). ^1H NMR (200MHz, DMSO-d^6) δ 9.03 (s, 1H), 8.70 (br s, 2H), 8.03 (s, 4H), 3.85 (s, 3H).

Example 40: 6-(4-carboxyphenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Step 1: 4-Acetylbenzoic acid (186 mg, 1.14 mmol) was dissolved in warm acetic acid (5 mL) and treated with bromine (58 mL, 1.14 mmol). The solution was stirred overnight before being cooled on ice. The resulting solid was filtered, washed with 1:1 methanol/water (3 x 10 mL) and dried *in vacuo* to provide 4-(2-bromoacetyl)benzoic acid as a white solid (102 mg). ^1H NMR (200MHz, DMSO-d^6) δ 8.07 (s, 4H), 4.98 (s, 2H).

Step 2: 4-(2-bromoacetyl)benzoic acid (102 mg) and 5-amino-1,3,4-thiadiazole-2-sulfonamide (75 mg, 0.42 mmol) were refluxed together in methanol (20 mL) for 48 hours. The resulting suspension was cooled to -10°C , filtered and the solid washed with cold methanol (3 x 5 mL) to provide compound 40 as a white crystalline solid (16 mg). ^1H NMR (200MHz, DMSO-d^6) δ 9.02 (s, 1H), 8.00 (s, 4H).

Example 41: 6-(3-cyanophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide
3-(2-bromoacetyl)benzonitrile (100 mg, 0.45 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (80 mg, 0.45 mmol) were refluxed in ethanol (10 mL) for 60 hrs. The

resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 98 as a white crystalline solid (78 mg, 57 %). ^1H NMR (200MHz, DMSO- d_6) δ 9.03 (s, 1H), 8.76 (s, 2H), 8.32 (s, 1H), 8.23 (d, $J = 7.6$ Hz, 1H), 7.71 (m, 2H); ^{13}C NMR (50 MHz, DMSO) δ 164.9, 145.8, 144.6, 134.6, 131.3, 130.2, 129.4, 128.3, 118.7, 112.4, 112.1.

Example 42: 6-(4-cyanophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide 4-(2-bromoacetyl)benzonitrile (448 mg, 2 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (360 mg, 2 mmol) were refluxed in ethanol for 60 hours. The resulting mixture was cooled on ice and the precipitate collected by suction filtration to provide 42 (300 mg) as a white powder. ^1H NMR (200MHz, DMSO- d_6) δ 9.07 (s, 1H), 8.77 (br s, 2H), 8.09 (d, 2H), 7.90 (d, 2H).

Example 43: 6-(4-(methylsulfonyl)phenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide
2-Bromo-1-[4-(methylsulfonyl)phenyl]ethan-1-one (100 mg, 0.36 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (65 mg, 0.36 mmol) were refluxed in ethanol (5 mL) for 60 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 43 as a white powder (55 mg, 43 %). ^1H NMR (200MHz, DMSO- d_6) δ 9.08 (s, 1H), 8.76 (s, 2H), 8.15 (d, $J = 8.1$ Hz, 2H), 7.96 (d, $J = 8.1$ Hz, 2H), 3.23 (s, 3H).

Example 44: 6-(4-(phenylmethylsulfonyl)phenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide
Compound 44 was prepared by bromination of 4'-(phenylmethylsulfonyl)acetophenone with bromine according to Method A, and condensation of the corresponding 2-bromoacetophenone with 2-amino-1,3,4-thiadiazole-5-sulfonamide, according to Method C, to yield compound 44 as a white solid. ^1H NMR (200MHz, DMSO- d_6) δ 9.06 (s, 1H), 8.74 (s, 2H), 8.02 (m, 6H), 7.65 (m, 3H).

Example 45:

Compound 44 was prepared by according to Methods A and C, to yield compound 45 as a white solid. ^1H NMR (200MHz, DMSO- d_6) δ 9.08 (s, 1H), 8.65 (s, 2H), 8.08 (d, $J=8.0$ Hz, 2H), 7.85 (d, $J=8.0$ Hz, 2H), 3.18 (quart, $J=7.6$ Hz, 2H), 1.05 (t, $J=7.6$ Hz, 3H).

Example 46: 6-(4-Pentylphenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide
2-Bromo-1-(4-pentylphenyl)ethan-1-one (269 mg, 1.0 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (180 mg, 1.0 mmol) were refluxed in ethanol (10 mL) for 48 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 46 as a white powder (180 mg, 51 %). ^1H NMR (200MHz, DMSO- d_6) δ 8.81 (s, 1H), 8.71 (s, 2H), 8.79 (d, $J = 8.2$ Hz, 2H), 7.24 (d, $J = 8.2$ Hz, 2H), 2.54 (t, $J = 7.0$ Hz, 2H), 1.57 (quintet, $J = 7.6$ Hz, 2H), 1.27 (m, 4H), 0.85 (t, $J = 6.7$ Hz, 3H); ^{13}C NMR (50 MHz, DMSO) : δ 164.0, 147.1, 145.3, 142.5, 130.9, 128.9, 125.2, 110.7, 34.9, 30.9, 30.6, 22.0, 14.0.

Example 47: 6-(4-Methylphenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide
2-Bromo-1-(4-methylphenyl)ethan-1-one (213 mg, 1 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (148 mg, 1 mmol) were refluxed in ethanol (10 mL) for 60 hours. Solvent was removed under reduced pressure. The suspension was cooled to -4°C , filtered and washed with cold methanol (3 x 5 mL), to provide compound 47 (118 mg, 42 %) as a white powder. ^1H NMR (200MHz, DMSO- d_6) δ 8.80 (s, 1H), 8.71 (s, 2H), 7.78 (d, 2H), 7.23 (d, 2H), 2.31 (s, 3H).

Example 48: 6-(2,4-dimethylphenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide
2-Bromo-1-(2,4-dimethylphenyl)ethan-1-one (227 mg, 1 mmol) and 2-amino-1,3,4-thiadiazole-2-sulfonamide (180 mg, 1 mmol) were refluxed in ethanol for 5 days. The volatiles were removed *in vacuo*. The residue was purified by column chromatography on silica using 30% ethyl acetate/1% acetic acid in hexane as eluant. Recrystallization from dichloromethane gave 48 (30 mg) as a white powder. ^1H NMR (200MHz, DMSO- d_6) δ 8.71 (br s, 2H), 8.52 (s, 1H), 7.70 (d, $J=7.6$ Hz, 1H), 7.10 (s, 1H), 7.06 (s, 1H), 2.46(s, 3H), 2.29 (s, 3H).

Example 49: 6-(4-(phenylmethylsulfonyl)phenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 44 was prepared by bromination of 4'-*tert*-butylacetophenone with bromine according to Method A, and condensation of the corresponding 2-bromoacetophenone with 2-amino-1,3,4-thiadiazole-5-sulfonamide, according to Method C, to yield compound 49 as a white solid. ^1H NMR (200MHz, DMSO- d^6) δ 8.81 (s, 1H), 8.70 (s, 2H), 7.81 (d, $J=7.9\text{Hz}$, 2H), 7.44 (d, $J=8.2\text{Hz}$, 2H), 1.29 (s, 9H).

Example 50

Compound 50 was prepared according to Method A and Method C, to yield compound 50 as a white solid. ^1H NMR (200MHz, DMSO- d^6) δ 8.72 (br s, 2H), 8.54 (s, 1H), 7.80 (s, 1H), 7.18 (s, 1H), 3.05 (t, 2H), 1.95 (t, 2H), 1.15 (s, 9H).

Example 51:

MS (m/z) M^+ =249.10

Example 52: 6-(4-(Trifluoromethyl)phenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-1-[4-(trifluoromethyl)phenyl]ethan-1-one (534 mg, 2.0 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (360 mg, 2.0 mmol) were refluxed in ethanol (10 mL) for 60 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 52 as a white powder (270 mg, 39 %). ^1H NMR (200MHz, DMSO- d^6) δ 9.05 (s, 1H), 8.74 (s, 2H), 8.10 (d, $J = 8.0\text{ Hz}$, 2H), 7.80 (d, $J = 8.0\text{ Hz}$, 2H).

Example 53: 6-(5-chloro-2-trifluoromethylphenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 51 was prepared by bromination of 5'-chloro-4'-trifluoromethylacetophenone with bromine according to Method A, and condensation of the corresponding 2-bromoacetophenone with 2-amino-1,3,4-thiadiazole-5-sulfonamide, according to Method

C, to yield compound 52 as a white solid. ^1H NMR (200MHz, DMSO- d_6) δ 9.04 (s, 1H), 8.78 (s, 2H), 8.47 (s, 1H), 7.82 (d, $J=8.6\text{Hz}$, 1H), 7.72 (d, $J=8.6\text{Hz}$, 1H).

Example 54: 6-(3,5-di(trifluoromethyl)phenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-1-[3,5-di(trifluoromethyl)phenyl]ethan-1-one (670 mg, 2.0 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (360 mg, 2.0 mmol) were refluxed in ethanol (10 mL) for 60 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 54 as a white powder (292 mg, 70 %). ^1H NMR (200MHz, DMSO- d_6) δ 9.26 (s, 1H), 8.77 (s, 2H), 8.54 (s, 2H), 8.04 (s, 1H).

Example 55: 6-(3,4-Di-*tert*-butyl-4-hydroxyphenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-1-(3,4-di-*tert*-butyl-4-hydroxyphenyl)ethan-1-one (327 mg, 1 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (148 mg, 1 mmol) were refluxed in ethanol (10 mL) for 60 hours. Solvent was removed under reduced pressure. The resulting solid was suspended in methanol (5 mL) and stirred for 30 minutes prior to suction filtration, washing twice for cold methanol (2 mL), to provide compound 55 (93 mg, 24 %) as a white powder. ^1H NMR (200MHz, DMSO- d_6) δ 8.72 (s, 1H), 8.68 (s, 2H), 7.63 (s, 2H), 1.41 (s, 9H).

Example 56: 6-(5,5,8,8-Tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-1-(5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)ethan-1-one (250 mg, 0.81 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (146 mg, 0.81 mmol) were refluxed in ethanol (10 mL) for 60 hours. Solvent was evaporated under reduced pressure and the resulting solid suspended in ethanol (3 ml). The precipitate was collected by suction filtration and washed with ethanol to provide compound 56 (45 mg) as an off white solid. ^1H NMR (200MHz, DMSO- d_6) δ 8.8 (s, 1H), 8.6 (br s, 2H), 7.8 (br s, 1H), 7.6 (dd, 1H), 7.3 (d, 1H), 1.6 (s, 4H), 1.3 (s, 6H), 1.2 (s, 6H).

Example 57:

¹H NMR (200MHz, DMSO-d⁶) δ 8.73 (s, 2H), 8.48 (s, 1H), 7.75 (s, 1H), 7.18 (s, 1H), 5.42 (br s, 4H), 2.21 (s, 3H), 1.63 (s, 3H), 1.23 (s, 9H).

Example 58: 6-(4-(*S*-1-acetamidoethyl)phenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-4'-(*S*-1-acetamidoethyl)acetophenone (426 mg, 1.5 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (222 mg, 1.5 mmol) were refluxed in ethanol (10 mL) for 60 hours. The resulting solution was cooled to -4 °C for 2 hours and the resulting solid was filtered, washing twice for cold methanol (2 mL), to provide compound 57 (172 mg, 34 %) as white crystals. ¹H NMR (200MHz, DMSO-d⁶) δ 8.82 (s, 1H), 8.70 (s, 2H), 8.28 (d, 1H), 7.83 (d, 2H), 7.34 (d, 2H), 4.91 (dt, 1H), 1.83 (s, 3H), 1.33 (d, 3H).

Example 59: 6-(4-(Trifluoromethyl)phenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-1-[4-(trifluoromethyl)phenyl]ethan-1-one (534 mg, 2.0 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (360 mg, 2.0 mmol) were refluxed in ethanol (10 mL) for 60 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 59 as a white powder (270 mg, 39 %). ¹H NMR (200MHz, DMSO-d⁶) δ 9.05 (s, 1H), 8.74 (s, 2H), 8.10 (d, J = 8.0 Hz, 2H), 7.80 (d, J = 8.0 Hz, 2H).

Example 60: 6-(1-adamantyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide
1-(1-Adamantyl)-2-bromoethan-1-one (514 mg, 2.0 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (360 mg, 2.0 mmol) were refluxed in ethanol (10 mL) for 60 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 60 as a white powder (120 mg, 18 %). ¹H NMR (200MHz, DMSO-d⁶) δ 8.64 (s, 2H), 8.03 (s, 1H), 2.03 (m, 3H), 1.90 (m, 6H), 1.72 (m, 6H).

Example 61: 6-(2-Naphthyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 61 was prepared by bromination of 1-acetylnaphthylene with bromine according to Method A, followed by condensation of the corresponding bromide with 2-amino-1,3,4-thiadiazole-5-sulfonamide, according to Method C, to yield an off white solid. ^1H NMR (200MHz, DMSO- d_6) δ 9.25 (br s, 2H), 8.79 (s, 1H), 8.77 (s, 1H), 8.63 (dd, 1H), 7.97 (m, 2H), 7.78 (dd, $J=1.2$, 7.0Hz, 1H), 7.61-7.49 (m, 3H).

Example 62: 6-(2-Naphthyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide
2-Bromonaphthone (2.50 g, 10.0 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (1.80 g, 1.2 mmol) were refluxed in 1,4-dioxane (20 mL) for 96 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 62 as a tan crystalline solid (2.36 g, 38 %) in two crops. ^1H NMR (200MHz, DMSO- d_6) δ 8.99 (s, 1H), 8.74 (br s, 2H), 8.42 (s, 1H), 8.05 (d, 1H), 7.96-7.89 (m, 2H), 7.51 (m, 2H).

Example 63: 6-(2-(6-methoxy-7-bromonaphthyl))imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Step 1: 2-Acetyl-6-methoxyacetophenone (1.00 g, 5.0 mmol) was dissolved in methanol (5 mL) and was treated with bromine (500 μL , 10.0 mmol). The reaction was stirred at room temperature for 2 hours before the volatiles were removed *in vacuo* to provide a 95:5 mixture of 2,7'-dibromo-6'-methoxynaphone and 2-acetyl-6-methoxyacetophenone. This crude mixture was advanced to the next step without further purification. ^1H NMR (200MHz, DMSO- d_6) δ 8.75 (s, 1H), 8.20 (d, 1H), 8.10 (d, 1H), 8.07 (dd, 1H), 7.64 (d, 1H), 5.01 (s, 2H), 4.03 (s, 3H).

Step 2: To the crude mixture obtained above was added 5-amino-1,3,4-thiadiazole-2-sulfonamide (740 mg, 5.0 mmol) and methanol (20 mL). The resulting suspension was refluxed for 48 hours, cooled on ice and the solid filtered off, to provide compound 63 as a white solid (230 mg). ^1H NMR (200MHz, DMSO- d_6) δ 8.95 (s, 1H), 8.76 (d, 1H), 8.44 (s, 1H), 8.11 (s, 2H), 8.02 (d, 1H), 7.52 (d, 1H), 3.99 (s, 3H).

Example 64: 6-pyrenylimidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

1-(Bromoacetyl)-pyrene (646mg, 2 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (360mg, 2 mmol) were refluxed in ethanol (20 ml) for 60 hrs. Solvent was removed under reduced pressure. The resulting solid was purified by silica gel chromatography, eluting with solvent gradient of 30-100% ethyl acetate/hexane, to afford compound 64 as a brownish orange solid (4.5 mg). ¹H NMR (200MHz, DMSO-d⁶) δ 9.0 (s, 1H), 8.8 (s, 2H), 8.50-8.00 (m, 9H).

Example 65: 5-Methyl-6-phenyl-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide
2-Bromopropiophenone (1.07 mg, 5.00 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide hydrochloride (900 mg, 5.0 mmol) were refluxed in ethanol (25 mL) for 48 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 65 as a white crystalline solid (100 mg). ¹H NMR (200MHz, DMSO-d⁶) δ 8.75 (br s, 3H), 7.75 (d, 2H), 7.45 (t, 2H), 7.30 (t, 1H), 2.65 (s, 3H).

Example 66: 5,6-Diphenyl-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide
2-Desyl bromide (550 mg, 2 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (360 mg, 2 mmol) were refluxed in ethanol (20ml) for 60 hrs. Solvent was removed under reduced pressure. Purification by silica gel chromatography, eluting with 30:0.1:70 ethyl acetate/ acetic acid/ hexane, and recrystallization from dichloromethane gave compound 66 as a white crystalline solid (175 mg). ¹H NMR (200MHz, DMSO-d⁶) δ 8.8-8.6 (s, 2H), 7.7-7.4 (m, 7H), 7.4-7.2 (m, 3H).

Example 67: 6-(4-Piperidinophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide
Step1: 4'-Piperidinoacetophenone (203 mg, 1.00 mmol) was dissolved in THF (5 mL) and treated with lithium bis(trimethylsilyl)amide (1.10 mL, 1.0M in THF, 1.10 mmol). The solution was stirred for 30 minutes prior to the addition of chlorotrimethylsilane (140 µL, 1.10 mmol). After stirring for an additional 30 minutes *N*-bromosuccinamide (300 mg, 1.73 mmol) was added and the mixture was refluxed for 4 hours. Standard aqueous/ethyl acetate workup provided a yellow solid which was further purified by silica gel chromatography, eluting with 3:1 hexane/ethyl acetate, to provide 2-

bromo-4'-piperidinoacetophenone as an off white solid (209 mg, 74 %). ¹H NMR (200MHz, CDCl₃) δ 8.75 (d, 2H), 6.84 (d, 2H), 4.61 (s, 2H), 3.40 (m, 4H), 1.68 (m, 6H).

Step 2: 2-Bromo-4'-piperidinoacetophenone (209 mg, 0.74 mol) and 5-amino-1,3,4-thiadiazole-2-sulfonamide (220 mg, 1.48 mmol) were suspended in 1,4-dioxane (10 mL) and refluxed for 48 hours. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography, eluting with 1:1 hexane/ethyl acetate, to provide compound 67 as a yellow solid (8.0 mg, 2.7 %). ¹H NMR (200MHz, DMSO-d₆) δ 8.68 (s, 3H), 7.75 (d, 2H), 6.98 (d, 2H), 3.23 (m, 4H), 1.57 (m, 6H).

Example 68: 6-(4-Morpholinophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Step 1: 4'-Morpholinoacetophenone (218 mg, 1.0 mmol) was dissolved in THF (5 mL) and treated with lithium bis(trimethylsilyl)amide (1.1 mL, 1.0M in THF, 1.1 mmol). The solution was stirred for 30 minutes prior to the addition of chlorotrimethylsilane (140 µL, 1.1 mmol). After stirring for an additional 30 minutes *N*-bromosuccinamide (300 mg, 1.73 mmol) was added and the mixture was refluxed for 4 hours. Standard aqueous/ethyl acetate workup provided a yellow solid, which was identified as a 3:1 mixture of 2-bromo-4'-morpholinoacetophenone and starting material. ¹H NMR (200MHz, CDCl₃) δ 7.86 (d, 2H), 6.84 (d, 2H), 4.62 (s, 2H), 3.84 (t, 4H), 3.32 (t, 4H).

Step 2: The crude 2-Bromo-4'-morpholinoacetophenone from above and 5-amino-1,3,4-thiadiazole-2-sulfonamide (100 mg, 0.66 mmol) were suspended in 1,4-dioxane (10 mL) and refluxed for 48 hours. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography, eluting with 1:1 hexane/ethyl acetate, to provide compound 68 as a yellow solid (23 mg). ¹H NMR (200MHz, DMSO-d₆) δ 8.67 (s, 3H), 7.74 (d, 2H), 6.99 (d, 2H), 3.75 (t, 4H), 3.13 (t, 4H).

Example 69: 6-(4-Benzoylamidophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Step 1: 4-Aminoacetophenone (1.35 g, 10.0 mmol) was dissolved in dichloromethane (10 mL) and treated with benzoyl chloride (1.74 mL, 15.0 mmol). The mixture was stirred for 16 hours at which time a white precipitate had formed. The solid was removed by filtration, washing with dichloromethane (3 x 20 mL) to provide 4-

acetamidoacetophenone as a white solid (2.74 g). ^1H NMR (200MHz, DMSO- d^6) δ 10.53 (s, 1H), 7.92 (s, 7H), 7.54 (m, 3H), 2.50 (s, 3H).

Step 2: 4-Benzoylamidoacetophenone (2.55 g) was dissolved in acetic acid (25 mL) and was treated with pyridinium tribromide (3.00 g, 8.0 mmol). The reaction was stirred at room temperature for 24 hours before the volatiles were removed *in vacuo* to provide 2-bromo-4'-benzoylamidoacetophenone. This crude mixture was advanced to the next step without further purification. ^1H NMR (200MHz, DMSO- d^6) δ 10.61 (s, 1H), 8.96 (d, 2H), 8.61 (t, 1H), 8.15-8.00 (m, 7H), 4.86 (s, 2H).

Step 3: To the crude mixture obtained above was added 5-amino-1,3,4-thiadiazole-2-sulfonamide (1.50 mg, 10.0 mmol) and methanol (20 mL). The resulting suspension was refluxed for 48 hours. The solvent was removed under reduced pressure and the residue was triturated from acetone to provide compound 69 as a yellow solid (120 mg). ^1H NMR (200MHz, DMSO- d^6) δ 10.35 (s, 1H), 8.82 (s, 1H), 8.70 (br s, 2H), 7.92 (d, 2H), 7.82 (s, 5H), 7.54 (d, 2H).

Example 70: 6-(4-Aminophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide
Compound 66 (60 mg) was suspended in methanol (10 mL) and treated with 6N HCl (1 mL). The suspension was refluxed for 16 hours until all solids had dissolved. The solvent was removed under reduced pressure and the residue was suspended in water (10 mL), neutralized with saturated aqueous NaHCO_3 . The resulting precipitate was extracted with ethyl acetate to provide compound 70 as a yellow solid (15 mg). ^1H NMR (200MHz, DMSO- d^6) δ 8.65 (br s, 2H), 8.53 (s, 1H), 7.58 (d, 2H), 6.58 (d, 2H), 5.32 (br s, 2H).

Example 71:

Compound 77 was prepared by the bromination of 4-acetylphenylboronic acid according to Method A to yield the desired a-bromoacetophenone, which was condensed with 2-amino-1,3,4-thiadiazole-5-sulfonamide according to Method C, to yield compound 71 as a white solid. ^1H NMR (200MHz, DMSO- d^6) δ 8.89 (s, 1H), 8.73 (s, 2H), 8.05 (br s, 2H), 7.86 (s, 4H).

Example 72: 6-(Biphenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-4'-phenylacetophenone (1.38 g, 5.0 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide hydrochloride (0.90 g, 5.0 mmol) were refluxed in ethanol (20 mL) for 60 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 72 as a white solid (0.75 g, 45 %). ¹H NMR (200 MHz, DMSO-d⁶) δ 8.95 (s, 1H), 8.74 (s, 2H), 8.00 (d, J = 8.6 Hz, 2H), 7.74 (m, 4H), 7.44 (m, 3H).

Example 73: 6-(4-(2,3,4,5,6-tetrafluorophenyl)phenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Step 1: 4'-Bromoacetophenone and 2,3,4,5,6-tetrafluorobenzene boronic (5.0 mmol) acid, K₂CO₃ (10 mmol), and PdCl₂(PPh)₂ (0.1 equiv) were refluxed in toluene for 16 hours. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography, eluting with 4:1 hexane/ethyl acetate, to provide 4'-(2,3,4,5,6-tetrafluorophenylacetophenone as a white solid.

Step 2: 4'-(2,3,4,5,6-Tetrafluorophenylacetophenone was dissolved in diethyl ether and treated with bromine (5 mmol). Solvent was removed under reduced pressure to provide 2-bromo-4'-(2,3,4,5,6-tetrafluorophenylacetophenone, which was used without further purification.

Step 3: 2-bromo-4'-(2,3,4,5,6-tetrafluorophenylacetophenone and 2-amino-1,3,4-thiadiazole-5-sulfonamide hydrochloride (0.90 g, 5.0 mmol) were refluxed in ethanol (20 mL) for 60 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 72 as a white solid (0.75 g, 45 %). ¹H NMR (200 MHz, DMSO-d⁶) δ 8.99 (s, 1H), 8.74 (s, 2H), 8.05 (d, J=8.6Hz, 2H), 7.57 (d, J=8.6Hz, 2H).

Example 74: 6-(4-(hydroxymethylphenyl)phenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 74 was prepared in a manner similar to compound 73.

¹H NMR (200 MHz, DMSO-d⁶) δ 8.93 (s, 1H), 8.73 (s, 2H), 7.98 (d, J=8.2Hz, 2H), 7.73 (d, J=8.2Hz, 2H), 7.67 (d, J=8.2Hz, 2H), 7.39 (d, J=8.2Hz, 2H), 4.53 (s, 2H).

Example 75: 6-(4-(2-methoxyphenyl)phenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 75 was prepared in a manner similar to compound 73.

¹H NMR (200MHz, DMSO-*d*⁶) δ 8.89 (s, 1H), 8.73 (s, 2H), 7.92 (d, J=8.3Hz, 2H), 7.53 (d, J=8.3Hz, 2H), 7.31 (m, 2H), 7.10 (d, J=8.5Hz, 1H), 7.02 (t, J=7.3Hz, 1H), 3.76 (s, 3H).

Example 76: 6-(4-(3-methoxyphenyl)phenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 76 was prepared in a manner similar to compound 73.

¹H NMR (200MHz, DMSO-*d*⁶) δ 8.94 (s, 1H), 8.73 (s, 2H), 7.97 (d, J=8.2Hz, 2H), 7.74 (d, J=8.3Hz, 2H), 7.34 (t, J=7.3Hz, 1H), 7.26 (d, J=7.3Hz, 1H), 7.23 (s, 1H), 6.92 (d, J=7.3Hz, 1H), 3.81 (s, 3H).

Example 77: 6-(4-(4-trifluoromethylphenyl)phenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 77 was prepared in a manner similar to compound 73.

¹H NMR (200MHz, DMSO-*d*⁶) δ 8.91 (s, 1H), 8.73 (s, 2H), 7.96 (d, J=8.6Hz, 2H), 7.70 (d, J=8.8Hz, 2H), 7.66 (d, J=8.6Hz, 2H), 7.02 (d, J=8.8Hz, 2H), 3.80 (s, 3H).

Example 78: 6-(4-(3-trifluoromethoxyphenyl)phenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 78 was prepared in a manner similar to compound 73.

¹H NMR (200MHz, DMSO-*d*⁶) δ 9.00 (s, 1H), 8.75 (s, 2H), 8.01 (d, J=8.0Hz, 2H), 7.79 (m, 3H), 7.69 (s, 1H), 7.59 (t, J=8.1Hz, 1H), 7.35 (d, J=7.9Hz, 1H).

Example 79: 6-(4-(hydroxymethylphenyl)phenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 79 was prepared in a manner similar to compound 73. MS (m/z) M+1 = 401

Example 80: 6-(4-(2-trifluoromethylphenyl)phenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 80 was prepared in a manner similar to compound 73.

^1H NMR (200MHz, DMSO- d^6) δ 8.93 (s, 1H), 8.71 (s, 2H), 7.95 (d, 2H), 7.77 (d, 2H), 7.66 (t, 1H), 7.60 (t, 1H), 7.35 (m, 2H).

Example 81: 6-(4-(3-trifluoromethylphenyl)phenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 81 was prepared in a manner similar to compound 73.

^1H NMR (200MHz, DMSO- d^6) δ 8.98 (s, 1H), 8.74 (s, 2H), 8.02 (m, 4H), 7.84 (d, $J=8.2\text{Hz}$, 2H), 7.70 (m, 2H).

Example 82: 6-(4-(4-trifluoromethylphenyl)phenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 82 was prepared in a manner similar to compound 73.

^1H NMR (200MHz, DMSO- d^6) δ 8.97 (s, 1H), 8.73 (s, 2H), 8.05-7.80 (m, 8H).

Example 83: 6-(4-(3,5-ditrifluoromethylphenyl)phenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 83 was prepared in a manner similar to compound 73.

^1H NMR (200MHz, DMSO- d^6) δ 9.02 (s, 1H), 8.75 (s, 2H), 8.38 (s, 2H), 8.01 (m, 5H).

Example 84: 6-(thiophen-2-yl-phenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 85 was prepared in a manner similar to compound 73.

^1H NMR (200MHz, DMSO- d^6) δ 8.92 (s, 1H), 8.70 (s, 2H), 7.94 (d, $J=8.2\text{Hz}$, 2H), 7.73 (d, $J=8.2\text{Hz}$, 2H), 7.56 (m, 2H), 7.15 (m, 1H).

Example 85: 6-(thiophen-3-yl-phenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 86 was prepared in a manner similar to compound 73.

^1H NMR (200MHz, DMSO- d^6) δ 8.79 (s, 1H), 8.72 (s, 2H), 7.88 (d, $J=8.2\text{Hz}$, 2H), 7.16 (t, $J=8.2\text{Hz}$, 1H), 7.03 (d, $J=8.2\text{Hz}$, 2H), 6.49 (d, $J=8.2\text{Hz}$, 1H), 6.38 (s, 1H), 6.27 (d, $J=7.3\text{Hz}$, 1H), 2.86 (s, 6H).

Example 86: 6-(thiophen-3-yl-phenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 86 was prepared in a manner similar to compound 73.

^1H NMR (200MHz, DMSO- d^6) δ 8.98 (s, 1H), 8.72 (s, 2H), 8.14 (s, 1H), 7.84 (d, $J=7.3\text{Hz}$, 1H), 7.67 (d, $J=8.5\text{Hz}$, 2H), 7.54 (m, 2H), 7.05 (d, $J=8.9\text{Hz}$, 2H), 2.80 (s, 3H).

Example 87: 6-(4-phenoxyphenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Step 1: 4-Phenoxyacetophenone was prepared by refluxing 4-fluoroacetone and phenol in DMAc for 16 hours. The solvent was removed under reduced pressure and the residue subjected to standard ethyl acetate/water work-up and the resulting material purified by silica gel chromatography.

Step 2: 4-Phenoxyacetophenone was brominated with bromine according to Method A to provide the desired α -bromoacetophenone, which was condensed with 2-amino-1,3,4-thiadiazole-5-sulfonamide according to method C, to provide compound 87 as an off white solid. ^1H NMR (200MHz, DMSO- d^6) δ 8.82 (s, 1H), 8.71 (s, 2H), 7.90 (d, $J=7.9\text{Hz}$, 2H), 7.40 (t, $J=7.3\text{Hz}$, 2H), 7.07 (t, $J=7.3\text{Hz}$, 1H), 7.08-7.03 (m, 6H).

Example 88: 6-(4-chlorophenoxyphenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 88 was prepared in a manner similar to compound 87.

^1H NMR (200MHz, DMSO- d^6) δ 8.81 (s, 1H), 8.72 (s, 2H), 7.89 (d, $J=8.5\text{Hz}$, 2H), 7.23 (m, 2H), 7.11-7.01 (m, 4H).

Example 89: 6-(4-(3,4-difluorophenoxy)phenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 89 was prepared in a manner similar to that described for compound 87. MS (m/z) M+1 = 409.

Example 90: 6-(4-(4-azaphenoxy)phenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 90 was prepared in a manner similar to that described for compound 87. ¹H NMR (200MHz, DMSO-d⁶) δ 9.02, 8.76 (s, 2H), 8.41 (d, J=8.6Hz, 2H), 8.10 (d, J=8.6Hz, 2H), 7.71 (d, J=8.6Hz, 2H), 7.01 (d, J=8.6Hz, 2H).

Example 91: 6-(4-chlorophenoxyphenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 91 was prepared in a manner similar to compound 87.

¹H NMR (200MHz, DMSO-d⁶) δ 8.84 (s, 1H), 8.72 (s, 2H), 7.92 (d, J=8.5Hz, 2H), 7.44 (d, J=8.5Hz, 2H), 7.08 (m, 4H).

Example 92: 6-(3,4-dichlorophenoxyphenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 92 was prepared in a manner similar to compound 87.

¹H NMR (200MHz, DMSO-d⁶) δ 8.86 (s, 1H), 8.72 (s, 2H), 7.94 (d, J=8.5Hz, 2H), 7.63 (d, J=8.9Hz, 1H), 7.34 (d, J=2.7Hz, 1H), 7.16 (d, J=8.9Hz, 2H), 7.04 (dd, ¹J=8.9Hz, ²J=2.8Hz, 1H).

Example 93: 6-(2-bromophenoxyphenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 93 was prepared in a manner similar to compound 87.

¹H NMR (200MHz, DMSO-d⁶) δ 8.82 (s, 1H), 8.72 (s, 2H), 7.90 (d, J=8.2Hz, 2H), 7.74 (d, J=7.9Hz, 1H), 7.37 (t, J=7.5Hz, 1H), 7.15 (t, J=8.4Hz, 2H), 7.00 (d, J=8.5Hz, 2H).

Example 94: 6-(3-bromophenoxyphenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 93 was prepared in a manner similar to compound 87. MS (m/z) M+1 = 452, M+2 = 454.

Example 95: 6-(4-bromophenoxyphenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 95 was prepared in a manner similar to compound 87. ¹H NMR (200 MHz, DMSO-*d*⁶) δ 6.98-7.19 (m, 4H), 7.55 (d, 2H, J = 8.5 Hz), 7.92 (d, 2H, J = 8.5 Hz), 8.71 (s, 2H), 8.84 (s, 1H).

Example 96: 6-(3-dimethylaminophenoxyphenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 96 was prepared in a manner similar to compound 87.

¹H NMR (200MHz, DMSO-*d*⁶) δ 8.79 (s, 1H), 8.72 (s, 2H), 7.88 (d, J=8.2Hz, 2H), 7.16 (t, J=8.2Hz, 1H), 7.03 (d, J=8.2Hz, 2H), 6.49 (d, J=8.2Hz, 1H), 6.38 (s, 1H), 6.27 (d, J=7.3Hz, 1H), 2.86 (s, 6H).

Example 97: 6-(4-(4-iso-propylphenoxy)phenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 97 was prepared in a manner similar to compound 87.

¹H NMR (200MHz, DMSO-*d*⁶) δ 8.81 (s, 1H), 8.72 (s, 2H), 7.89 (d, J=8.9Hz, 2H), 7.26 (d, J=8.5Hz, 2H), 7.03 (d, J=8.9Hz, 2H), 6.97 (d, J=8.5Hz, 2H), 2.88 (septet, J=6.9Hz, 1H), 1.19 (d, J=6.7Hz, 6H).

Example 98: 6-(4-(4-azaphenoxy)phenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 98 was prepared in a manner similar to that described for compound 87. ¹H NMR (200MHz, DMSO-*d*⁶) δ 8.79 (s, 1H), 8.71 (s, 2H), 7.84 (d, J=8.8Hz, 2H), 7.06-6.94 (m, 4H), 3.74 (s, 3H).

Example 99: 6-(4-(4-nitrophenoxy)phenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 99 was prepared in a manner similar to compound 87.

^1H NMR (200MHz, DMSO- d^6) δ 8.91 (s, 1H), 8.73 (s, 2H), 8.25 (d, $J=8.9\text{Hz}$, 2H), 8.00 (d, $J=8.2\text{Hz}$, 2H), 7.27 (d, $J=8.5\text{Hz}$, 2H), 7.18 (d, $J=8.9\text{Hz}$, 2H).

Example 100: 6-(3-bromophenoxyphenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 100 was prepared in a manner similar to compound 87. MS (m/z) $M+1 = 409$.

Example 101:

Step 1: 4-Hydroxyacetophenone (5.00 g, 36.7 mmol) was dissolved in THF (100 mL) and cooled on ice. Sodium bis(trimethylsilyl)amide (40.5 mL, 1.0M in THF, 40.5 mmol) was added and the solution was warmed to room temperature. After stirring for 2 hours the solution was cooled on ice and ethyl bromoacetate (6.14 mL, 55.1 mmol) was added. The solution was stirred over night. Standard aqueous workup provided the desired ester as a clear oil, which was dissolved in 3:2:1 THF/methanol/1.0M NaOH (36 mL). After stirring over night the solution was diluted with diethyl ether and water. The aqueous layer was separated, washed with diethyl ether, and acidified. The resulting solid was extracted with ethyl acetate to provide 2-(4-acetylphenoxy)acetic acid as a white solid (2.91 g).

Step 2: 2-(4-acetylphenoxy)acetic acid (2.81 g, 14.5 mmol) was dissolved in acetic acid (100 mL) and treated with bromine (740 μL , 14.5 mmol) and stirred 48 hours. Bromine (370 mL, 7.25 mmol) was added and solution was stirred for an additional 16 hours. Volatiles were removed under reduced pressure to provide a brown solid which was titrated with diethyl ether to provide 2-(4-(2-bromoacetyl)phenoxy)acetic acid (1.82 g) as a light brown solid.

Step 3: 2-(4-(2-Bromoacetyl)phenoxy)acetic acid (1.00 g, 3.66 mmol) and 5-amino-1,3,4-thiadiazole-2-sulfonamide (659 mg, 3.66 mmol) were refluxed together in methanol (20 mL) for 48 hours. The resulting suspension was cooled to $-10\text{ }^\circ\text{C}$, filtered and the solid washed with cold methanol (3 x 5 mL) to provide compound 101 as a white crystalline solid (578 mg, 44 %). ^1H NMR (200MHz, DMSO- d^6) δ 8.69 (s, 1H), 7.65 (d, 2H), 7.02 (d, 2H), 4.83 (s, 2H), 3.70 (s, 3H), 2.64 (s, 3H).

Example 102:

Compound 101 (50 mg, 0.14 mmol) was dissolved in 3:2:1 THF/methanol/1M NaOH (9 mL) and stirred over night. The resulting solution was diluted with ethyl acetate and water. The aqueous layer was washed with ethyl acetate and acidified to yield a white suspension. The suspension was extracted with ethyl acetate, the organic layer was dried over anhydrous MgSO_4 , filtered, and the solvent removed under reduced pressure to provide compound 102 as a white solid (10.2 mg). ^1H NMR (200MHz, DMSO-d_6) δ 8.74 (s, 1H), 7.80 (d, $J=8.8\text{Hz}$, 2H), 6.96 (d, $J=8.8\text{Hz}$, 2H), 4.66 (s, 2H).

Example 103:

4-(2-Bromopropionyl)phenylacetic acid (256 mg, 1.0 mmol) and 5-amino-1,3,4-thiadiazole-2-sulfonamide (185 mg, 1.22 mmol) were refluxed together in methanol (20 mL) for 48 hours. The resulting suspension was cooled to -10°C , filtered and the solid washed with cold methanol (3 x 5 mL) to provide compound 103 as a white crystalline solid (22 mg, 7 %). ^1H NMR (200MHz, DMSO-d_6) δ 8.69 (s, 1H), 7.65 (d, 2H), 7.02 (d, 2H), 4.83 (s, 2H), 3.70 (s, 3H), 2.64 (s, 3H).

Example 104: 6-(3-chloro-4-methylphenyl)-5-methylimidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-1-(3-chloro-4-methylphenyl)propan-1-one (262 mg, 1.0 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (180 mg, 1.0 mmol) were refluxed in ethanol (10 mL) for 5 days. The resulting solution was concentrated and the crude material was purified by column chromatography on silica gel, eluting with 25:75 ethyl acetate/hexanes to provide compound 104 as a yellow powder (38 mg, 11 %). ^1H NMR (200MHz, DMSO-d_6) δ 8.72 (s, 2H), 7.74 (m, 1H), 7.59 (m, 1H), 7.48 (m, 1H), 2.68 (s, 3H), 2.39 (s, 3H).

Example 105: 6-(2-Pyridyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-(2-bromoacetyl)pyridine (2.5 g, 12.4 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (2.2 g, 12.4 mmol) were refluxed in methanol (75 mL) for 48 hrs. After evaporation of methanol 1M sodium hydroxide (25 mL) was added and the resulting

solution was washed with ether (3 x 20 mL). The aqueous layer was acidified to a pH of 7 with 1M hydrochloric acid and extracted with ethyl acetate (3 x 25 mL). The solid obtained from the organic layers was recrystallized in acetone to provide compound 105 as a light brown powder (84 mg, 2.4 %). ¹H NMR (200MHz, DMSO-d⁶) δ 8.82 (s, 1H), 8.74 (br s, 2H), 8.58 (d, J = 5.5 Hz, 1H), 7.92 (m, 2H), 7.33 (m, 1H).

Example 106: 6-(2-Pyridyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide HCl
Compound 105 (25 mg) was dissolved in methanol and HCl gas was bubbled through for 30 seconds. Volatiles were removed under reduced pressure to provide a white solid (99%). ¹H NMR (200MHz, D₂O-d⁶) δ 8.86 (s, 1H), 8.57 (d, J=5.8Hz, 1H), 8.50 (t, J=7.5Hz, 1H), 8.27 (d, J=8.2Hz, 1H), 7.80 (t, J=6.7Hz, 1H).

Example 107: 6-(4-Pyridyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide
2-Bromo-1-(4-pyridinyl)-1-ethanone hydrobromide (100 mg, 0.356 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (64 mg, 0.356 mmol) were refluxed in 1,4-dioxane (5 mL) for 48 hours. The resulting solid was isolated by filtration and recrystallized from methanol to provide compounds 80 as a brown solid (129 mg, 42 % yield). ¹H NMR (200MHz, DMSO-d⁶) δ 9.52 (s, 1H), 8.90 (d, 2H), 8.84 (s, 2H), 8.39 (d, 2H).

Example 108: 6-(2-Pyrimidenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Step 1: Acetylpyrazine (244 mg, 2.0 mmol) was suspended in glacial acetic acid (10 mL) and treated with pyridinium tribromide (640 mg, 2.0 mmol). The reaction mixture was stirred overnight. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography, eluting with 1:1 hexane/ethyl acetate, to provide 2-(2-bromoacetyl)pyrazine as a brown solid (154 mg, 38%). ¹H NMR (200MHz, DMSO-d⁶) δ 9.16 (d, J = 1.5Hz, 1H), 8.94 (d, J = 2.4Hz, 1H), 8.82 (dd, J = 1.5, 2.4Hz, 1H), 4.99 (s, 2H).

Step 2 2-(2-Bromoacetyl)pyrazine (154 mg, 0.764 mmol) and 5-amino-1,3,4-thiadiazole-2-sulfonamide (138 mg, 0.764 mmol) were refluxed together in methanol (10 mL) for 48 hours. The resulting suspension was cooled to -10 °C, filtered and the solid washed with cold methanol (3 x 2 mL) to provide compound 108 as a brown solid (6.6

mg, 3.1%). ^1H NMR (200MHz, DMSO- d^6) δ 9.19 (s, 1H), 8.98 (s, 1H), 8.78 (s, 2H), 8.65 (d, $J = 1.5\text{Hz}$, 1H), 8.59 (d, $J = 2.7\text{Hz}$, 1H).

Example 109: 6-(coumaran-2-yl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide 2-(2-Bromoacetyl)coumaran (mg, 1.0 mmol) and 5-amino-1,3,4-thiadiazole-2-sulfonamide (180 mg, 1.0 mmol) were refluxed together in methanol (10 mL) for 72 hours. The resulting suspension was cooled to -10°C , filtered and the solid washed with cold methanol (3 x 2 mL) to provide compound 92 as a white solid (15.6 mg, 5.4%). ^1H NMR (200MHz, DMSO- d^6) δ 8.79 (s, 1H), 8.65 (br s, 1H), 8.61 (s, 1H), 7.81 (d, $J=7.6\text{Hz}$, 1H), 7.58 (m, 1H), 7.38 (m, 2H). ^{13}C NMR (50MHz, DMSO- d^6) δ 164.7, 158.5, 152.5, 139.9, 137.5, 131.9, 128.9, 124.8, 119.8, 119.1, 116.0, 114.6, 96.7.

Example 110:

6-(Chloroacetyl)-2-*H*-1,4-benzoxazin-3(4*H*)-one (248 mg, 1.1 mmol), *n*-Bu₄NI (405 mg, 1.1 mmol) and 5-amino-1,3,4-thiadiazole-2-sulfonamide (148 mg, 1.0 mmol) were refluxed together in methanol (12 mL) for 4 days. The resulting precipitate was isolated by filtration, washing with cold methanol, to provide compounds 110 as a white solid (58. mg). ^1H NMR (200MHz, DMSO- d^6) δ 10.84 (s, 1H), 8.79 (s, 3H), 7.48 (s, 1H), 7.42 (d, 2H), 7.00 (d, 2H), 4.58 (s, 2H).

Example 111: 6-(Benzo[*b*]furan-2-yl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide 1-(1-benzofuran-2-yl)-2-bromoethan-1-one (100 mg, 0.41 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (74 mg, 0.41 mmol) were refluxed in ethanol (5 mL) for 30 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 111 as an off white powder (47 mg, 33 %). ^1H NMR (200MHz, DMSO- d^6) δ 8.86 (s, 1H), 8.77 (br s, 2H), 7.65 (m, 2H), 7.29 (m, 3H).

Example 112: 6-(2-Thiophenyl)-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide 2-Acetylthiophene (252 mg, 2.0 mmol) was dissolved in acetic acid (5 mL) and treated with bromine (100 μL , 2.0 mmol). The solution was stirred overnight before the volatiles

were removed under reduced pressure to provide a white solid, which contained a 3:1 mixture of (2-bromoacetyl)thiophene and starting material. This crude mixture was refluxed in methanol (10 mL) with 5-amino-1,3,4-thiadiazole-2-sulfonamide (300 mg, 2.0 mmol) for 5 days. The resulting solid was filtered, washing with methanol (3 x 5 mL) to provide compounds 112 as a light pink solid (60.5 mg). ^1H NMR (200MHz, DMSO- d_6) δ 8.70 (s, 1H), 7.48 (m, 2H), 7.11 (t, 1H).

Example 113: 6-(5-Phenylthiophen-2-yl)-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide
2-Bromo-1-(5-phenyl-2-thienyl)-1-ethanone (100 mg, 0.36mmol) and 2-amino-1,3,4-thiadiazole-2-sulfonamide were refluxed in ethanol for 120 hours. The volatiles were removed *in vacuo*. The residue was purified by column chromatography on silica gel using 20% ethyl acetate/1% acetic acid in hexane followed by 30% ethyl acetate/1% acetic acid in hexane as eluant. Triturating with diethyl ether provided compound 113 (7 mg) as an orange solid. ^1H NMR (200MHz, DMSO- d_6) δ 8.82 (s, 1H), 8.70 (br s, 2H), 7.70-7.20 (m, 7H).

Example 114: 5-Bromo-6-(5-Nitro-2-thiophenyl)-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide hydrobromide

Example 115: 6-(3-Methylbenzo[*b*]thiophen-2-yl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-1-(3-methylbenzo[*b*]thiophen-2-yl)ethan-1-one (125 mg, 0.5 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (74 mg, 0.5 mmol) were refluxed in ethanol (10 mL) for 72 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 115 as a white crystalline solid (63 mg, 39 %). ^1H NMR (200MHz, DMSO- d_6) δ 8.80 (s, 1H), 8.78 (s, 2H), 8.94 (dd, 1H), 8.83 (dd, 1H), 7.42 (dt, 1H), 7.37 (dt, 1H), 2.58 (s, 3H).

Example 116: 6-(Benzo[*b*]thiophen-3-yl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

1-Benzo[b]thiophen-3-yl-2-bromoethan-1-one (125 mg, 0.5 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (74 mg, 0.5 mmol) were refluxed in ethanol (10 mL) for 72 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 116 as a white crystalline solid (63 mg, 39 %). ¹H NMR (200MHz, DMSO-d⁶) δ 8.91 (s, 1H), 8.74 (br s, 2H), 8.52 (d, 1H), 8.13 (s, 1H), 8.05 (d, 1H), 7.50-7.42 (m, 2H).

Example 117: 6-(4-Phenylisoxazol-3-yl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Prepared according to Method C. ¹H NMR (200MHz, DMSO-d⁶) δ 9.03 (s, 1H), 8.79 (s, 2H), 7.95 (m, 3H), 7.53 (m, 2H), 7.36 (s, 3H).

Example 118: 6-(5-Methyl-3-phenylisoxazol-4-yl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-1-(5-methyl-3-phenylisoxazol-4-yl)ethan-1-one (100 mg, 0.36 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (65 mg, 0.36 mmol) were refluxed in ethanol (5 mL) for 60 hrs. Solvent was evaporated and the crude solid was purified by flash chromatography using 35 : 65 ethyl acetate : hexanes to provide compound 118 as a yellowish powder (64 mg, 50 %). ¹H NMR (200MHz, DMSO-d⁶) δ 8.73 (br s, 2H), 8.25 (s, 1H), 7.58 (m, 2H), 7.45 (m, 3H), 2.56 (s, 3H).

Example 119: 6-(Ethyl isoxazol-5-yl-3-carboxylate)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Ethyl 5-(2-bromoacetyl)isoxazole-3-carboxylate (100 mg, 0.38 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (70 mg, 0.38 mmol) were refluxed in ethanol (5 mL) for 60 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 229-053 as an orange powder (21 mg, 16 %). ¹H NMR (200MHz, DMSO-d⁶) δ 9.14 (s, 1H), 8.82 (s, 2H), 7.16 (s, 1H), 4.39 (q, J = 7.0 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H).

Example 120: 6-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-1-(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethan-1-one (100 mg, 0.36 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (65 mg, 0.36 mmol) were refluxed in ethanol (5 mL) for 45 hrs. Solvent was evaporated and the solid was recrystallized from ethanol to provide compound 120 as a beige powder (30 mg, 28 %). ¹H NMR (200MHz, DMSO-*d*⁶) δ 8.71 (s, 2H), 8.55 (s, 1H), 7.98 (s, 1H), 7.52 (m, 5H), 2.56 (s, 3H).

Example 121: 6-(Thiaxol-2-yl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Step1 2-Acetylthiazole (400 μL, 3.86 mmol) was suspended in chloroform (10 mL) and treated with pyridinium tribromide (1.23 g, 3.86 mmol). The reaction mixture was stirred for two days. The solvent was removed under reduced pressure. Standard aqueous/ethyl acetate workup provided a dark orange solid, which was identified as a 8:1 mixture of 2-(2-bromoacetyl)thiazole and starting material. ¹H NMR (200MHz, DMSO-*d*⁶) δ 8.30 (d, *J* = 2.1Hz, 1H), 8.18 (d, *J* = 2.1Hz, 1H), 4.93 (s, 2H).

Step 2 2-(2-Bromoacetyl)thiazole (206 mg, 1.0 mmol) and 5-amino-1,3,4-thiadiazole-2-sulfonamide (180mg, 1.0 mmol) were refluxed together in methanol (10 mL) for 72 hours. The resulting suspension was cooled to -10 °C, filtered and the solid washed with cold methanol (3 x 2 mL) to provide compound 121 as a white solid (15.6 mg, 5.4%). ¹H NMR (200MHz, DMSO-*d*⁶) δ 8.90 (s, 1H), 8.74 (br s, 2H), 7.90 (d, *J* = 3.1Hz, 1H), 7.75 (d, *J* = 3.3Hz, 1H).

Example 122: 6-(2,4-Thiaxol-5-yl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 122 was prepared according to the method described for compound 103 to provide compound 122 as an off white solid. ¹H NMR (200MHz, DMSO-*d*⁶) δ 8.74 (s, 2H), 8.65 (s, 1H), 2.63 (s, 3H), 2.47 (s, 3H).

Example 123: 5-Chloro-6-phenyl-imidazo[2,1-*b*]-1,3,4-thiadiazole-sulfonamide

Compound 1 (250 mg, 0.891 mmol) was dissolved in 10:1 THF/water (22 mL) and treated with 40 % sodium hypochlorite (1 mL). The solution was stirred for 3 hours before the

volatiles were removed under reduced pressure to provide a light yellow solid (310 mg, 98%). ^1H NMR (200MHz, DMSO- d_6) δ 7.96 (m, 2H), 7.43 (t, 2H), 7.39 (t, 1H).

Example 124: 5-Bromo-6-phenyl-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide hydrobromide

Compound 1 (5.00 g, 17.8 mmol) in AcOH (200 mL) was treated with bromine (0.96 mL, 18.7 mmol). The solution was stirred overnight and the formation of a white precipitate was observed. The solvent was evaporated and the solid was suspended in MeOH (50 mL). That suspension was put in the fridge for one hour and filtered to provide compound 12 as a white powder (4.8 g, 76 % after 3rd crop). ^1H NMR (200 MHz, DMSO) : δ 8.82 (s, 2H), 7.98 (d, J = 8.2 Hz, 2H), 7.46 (m, 3H).

Example 125: 5-Bromo-6-(2-pyridyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide hydrobromide

Compound 105 (50 mg, 0.18 mmol) was suspended in acetic acid (5 mL) and treated with bromine (10 μL , 0.20 mmol). After stirring overnight the volatiles were removed under reduced pressure and the solid was dried under vacuum to provide compound 125 as a yellow solid (54 mg, 84 %). ^1H NMR (200MHz, DMSO- d_6) δ 8.84 (s, 2H), 8.67 (d, J = 4.6 Hz, 1H), 8.02 (m, 2H), 7.43 (m, 1H); ^{13}C NMR (50 MHz, DMSO) δ 166.9, 147.1, 146.0, 142.6, 137.9, 124.8, 122.4, 98.7.

Example 126: 5-Bromo-6-(4-nitrophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide hydrobromide

Example 127: 5-Bromo-6-(4-chlorophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide hydrobromide

Example 128: 5-Bromo-6-(4-bromophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide hydrobromide

Compound 14 (100 mg, 0.278 mmol) was suspended in acetic acid (5 mL) and treated with neat bromine (16 μ L, 0.306 mmol). The reaction mixture was stirred overnight and volatiles were removed under reduced pressure to provide compounds 128 as a light orange solid (143 mg, 99%). ^1H NMR (200MHz, DMSO- d_6) δ 8.82 (s, 2H), 7.92 (d, 2H), 7.68 (d, 2H).

Example 129: 5-Bromo-6-(2-bromo-3-methoxyphenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide hydrobromide

Prepared according to the method described for compound 128.

Example 130: 5-Bromo-6-(2-naphthyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide hydrobromide

Compound 62 (192 mg, 0.582 mmol) was suspended in acetic acid (10 mL) and treated with neat bromine (31 μ L, 0.612 mmol). After stirring overnight the volatiles were removed under reduced pressure, to provide compound 130 as a tan solid (279 mg, 93 %). ^1H NMR (200MHz, DMSO- d_6) δ 8.83 (br s, 2H), 8.42 (s, 1H), 8.04 (d, 1H), 7.98-7.80 (m, 3H), 7.48 (m, 2H).

Example 131: 5-Chloro-6-(biphenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide hydrobromide

Compound 131 was prepared according to the method described for compound 123 to provide a white solid.

Example 132: 5-Bromo-6-(biphenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide hydrobromide

Compound 72 (1.00 g, 2.80 mmol) was suspended in AcOH (20 mL) and treated with bromine (172 μ L, 3.4 mmol). The solution was stirred overnight and the formation of a white precipitate was observed. The solvent was evaporated and the solid was dissolved in 10 mL MeOH. That suspension was put in the fridge for one hour to increase precipitation. Successive precipitations and filtrations provided compound 132 as a yellow powder (1.10

g, 79 %). ^1H NMR (200 MHz, DMSO) δ 8.82 (s, 1H), 8.11 (d, J = 8.5 Hz, 2H), 7.82 (d, J = 8.6 Hz, 2H), 7.74 (d, J = 8.5 Hz, 2H), 7.45 (m, 3H).

Example 133: 5-Bromo-6-(5-nitrothiophen-2-yl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide hydrobromide

Example 134: 5-Bromo-6-trifluoromethylimidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 74 (430 mg, 1.59 mmol) was suspended in acetic acid (10 mL) and treated with bromine (244 μL , 4.76 mmol). After stirring overnight the volatiles were removed under reduced pressure to provide a 1:1 mixture of compounds 74 and 75. The above process was repeated to provide compound 134 as a white solid (477 mg). ^1H NMR (200MHz, DMSO- d_6) δ 8.89 (s, 2H).

Example 135: 5-Thiophenyl-6-(2-naphthyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 130 (100 mg, 0.204 mmol) and mercaptobenzene (28 μL , 0.269 mmol) were combined in THF (10 mL) and refluxed for 16 hours, followed by 72 hours at room temperature. Volatiles were removed under reduced pressure and the resulting residue was triturated with diethyl ether to provide compound 135 as a yellow solid (62 mg, 69 % yield). ^1H NMR (200MHz, DMSO- d_6) δ 8.82 (br s, 2H), 8.58 (s, 1H), 8.19 (d, 1H), 7.92 (d, 1H), 7.83 (m, 2H), 7.53 (m, 2H), 7.38-7.12 (m, 5H).

Example 136: 5-(*S*-(2-Thio-5-amino-1,3,4-thiadiazolyl)-6-(2-naphthyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

Compound 130 (102 mg, 0.208 mmol) and 5-amino-1,3,4-thiadiazole-2-thiol (37 mg, 0.275 mmol) were combined in a 2:1 mixture of ethyl acetate/methanol (15 mL) and refluxed for 16 hours, followed by 72 hours at room temperature. Volatiles were removed under reduced pressure and the resulting residue was recrystallized from methanol to provide compound 136 as a yellow solid (32 mg, 34 % yield). ^1H NMR (200MHz,

DMSO- d_6) δ 8.86 (br s, 2H), 8.66 (s, 1H), 8.28 (d, 1H), 8.02 (d, 1H), 7.98 (m, 2H), 7.57 (m, 2H), 7.36 (br s, 2H).

Example 137: 6-Phenyl-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-*N*-methylsulfonamide

Compound 1 (110 mg, 0.50 mmol), methanol (30 mg, 0.5 mmol), and triphenylphosphine (130 mg, 0.5 mmol) were combined in THF (5 mL). This solution was added to a reaction vessel containing polymer supported DIAD (500 mg, 0.50 mmol). After being shaken overnight, the solid resin was removed by filtration and the filtrate was concentrated under reduced pressure. The resulting semi-solid was purified by silica gel chromatography, eluting with 10% ethyl acetate/hexane, to provide compound 137 as a white solid. ^1H NMR (200MHz, acetone- d_6) δ 8.58 (s, 1H), 7.98 (d, 2H), 7.42 (t, 2H), 7.31 (t, 1H), 2.93 (s, 3H).

Example 138: 6-(2,3,4,5,6-pentafluorophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-*N*-methylsulfonamide

MS (m/z) $M+1 = 385$.

Example 139: 6-Phenyl-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-*N,N*-dimethylsulfonamide

Compound 1 (140 mg, 0.5 mmol), methanol (64 mg, 2.0 mmol), and triphenylphosphine (525 mg, 2.0 mmol) were combined in THF (2 mL) and treated with DIAD (200 μL , 2.0 mmol). The resulting solution was stirred over night. The resulting solid was filtered and washed with THF (2 x 3 mL) to provide compound 4 as a white crystalline solid. ^1H NMR (200MHz, DMSO- d_6) δ 8.92 (s, 1H), 8.91 (d, 2H), 7.44 (t, 2H), 7.34 (t, 1H), 2.93 (s, 6H).

Example 140: 6-(2,3,4,5,6-pentafluorophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-*N,N*-dimethylsulfonamide

Compound 140 was preped in a manner similar to compound 138. ^1H NMR (200MHz, DMSO- d_6) δ 8.86 (t, 1H), 2.95 (s, 6H).

Example 141: 6-(3-Methoxyphenyl-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-*N,N*-diethylsulfonamide

Compound 16 (50 mg, 0.162 mmol), ethanol (28 μ L, 0.486 mmol), and triphenylphosphine (127 mg, 0.86 mmol) were combined in THF (10 mL) and treated with DIAD (96 μ L, 0.468 mmol). The resulting solution was stirred over night. Solvent was removed under reduced pressure and the resulting semi-solid was triturated with diethyl ether to provide compound 141 as a white crystalline solid (19.6 mg, 33 %). ^1H NMR (200MHz, CDCl_3) δ 8.06 (s, 1H), 7.38 (d, 2H), 7.35 (t, 1H), 6.88 (d, 1H), 3.88 (s, 3H), 3.45 (q, 4H), 1.35 (t, 6H).

Example 142: 6-(3-Methoxyphenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-*N,N*-dibutylsulfonamide

Compound 16 (50 mg, 0.162 mmol), butanol (44 μ L, 0.486 mmol), and triphenylphosphine (127 mg, 0.486 mmol) were combined in THF (10 mL) and treated with DIAD (96 μ L, 0.486 mmol). The resulting solution was stirred over night. The solvent was removed under reduced pressure and the resulting semi-solid was purified by silica gel chromatography, eluting with 10 % ethyl acetate/hexane, to provide compound 142 as a light yellow solid (49 mg, 72 %). ^1H NMR (200MHz, CDCl_3) δ 8.08 (s, 1H), 7.38 (d, 2H), 7.35 (t, 1H), 3.89 (s, 3H), 3.34 (t, 4H), 1.67 (m, 4H), 1.36 (m, 3H), 0.93 (t, 6H).

Example 143: 6-(4-Bromophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-*N,N*-dimethylsulfonamide

Compound 143 was prepared from compound 14 according to the method described for compound 142.

Example 144: 6-(4-Bromophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-*N,N*-dimethylsulfonamide hydrobromide

6-(4-Bromophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-*N,N*-dimethylsulfonamide (100 mg, 0.258 mmol) was suspended in acetic acid (5 mL) and treated with neat bromine (18 μ L, 0.315 mmol). The reaction mixture was stirred overnight and volatiles were removed

under reduced pressure to provide compounds 144 as a light orange solid (140 mg, 99%).
 ^1H NMR (200MHz, DMSO- d^6) δ 7.84 (d, 2H), 7.63 (d, 2H), 2.93 (s, 6H).

Example 145: 6-(3-Hydroxyphenyl-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-*N,N*-dimethylsulfonamide

Step 1: Compound 16 (212 mg, 0.851 mmol), methanol (103 μL , 2.55 mmol), and triphenylphosphine (669 mg, 2.55 mmol) were combined in THF (10 mL) and treated with DIAD (502 μL , 2.55 mmol). The resulting solution was stirred over night. Solvent was removed under reduced pressure and the resulting semi-solid was triturated with methanol to provide white crystalline solid (244 mg, 85 %). ^1H NMR (200MHz, DMSO- d^6) δ 8.12 (s, 1H), 7.40 (dd, 1H), 7.38 (d, 1H), 7.33 (t, 1H), 6.88 (ddd, 1H), 3.87 (s, 3H), 3.02 (s, 6H).

Step 2: The above compound (420 mg, 1.24 mmol) was suspended in methylenechloride (10 mL) and treated with a BBr_3 (6.20 mL, 1.0M in CH_2Cl_2 , 6.20 mmol). The reaction mixture was stirred overnight before being quenched with water (1 mL), followed by saturated NaHCO_3 (10 mL). The resulting mixture was diluted with ethyl acetate (20 mL) and subjected to standard workup. The organic layer provided a off yellow solid which was further purified by recrystallization from methanol to provide compounds 49 was a gray solid (14 mg, 32 %). ^1H NMR (200MHz, DMSO- d^6) δ 9.50 (br s, 1H), 8.83 (s, 1H), 7.30 (m, 2H), 7.25 (t, 1H), 6.71 (dd, 1H), 2.93 (s, 6H).

Example 146: 6-(3-Benzoyloxyphenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-*N,N*-dimethylsulfonamide

Compound 145 (20 mg, 0.062 mmol) was dissolved in THF (2 mL) and treated with triethylamine (10 mL, 0.068 mmol) followed by benzoyl chloride (9 mL, 0.068 mmol). The reaction mixture was stirred for 4 hours before a second equiv of triethylamine and benzoyl chloride were added. Standard aqueous workup and purification by silica gel chromatography, eluting with 30% ethyl acetate/hexane, provided compound 146 as a white solid (16 mg, 62 %). ^1H NMR (200MHz, CDCl_3) δ 8.22 (m, 2H), 8.12 (s, 1H), 7.77-7.60 (m, 3H), 7.58-7.44 (m, 3H), 7.22 (m, 1H).

Example 147: 6-(2-Naphthyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-*N,N*-dimethylsulfonamide

Compound 62 (330 mg, 1.0 mmol), methanol (180 μ L, 4.40 mmol), and triphenylphosphine (1.15 g, 4.40 mmol) were combined in THF (10 mL) and treated with DIAD (1.90 mL, 4.40 mmol). The resulting solution was stirred over night. The solvent was removed under reduced pressure and the resulting semi-solid was triturated with diethyl ether, to provide compound 147 as a white crystalline solid (268 mg, 75 %). ^1H NMR (200MHz, DMSO- d_6) δ 9.02 (s, 1H), 8.45 (s, 1H), 8.07-7.83 (m, 3H), 7.56 (m, 2H), 2.91 (s, 6H).

Example 148: 6-Phenyl-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide sodium salt
Compound 1 (200 mg, 0.71 mmol) was added to a solution of sodium hydroxide (28 mg, 0.71 mmol) in 4:1 MeOH/H₂O (5 mL). The solution was stirred overnight at room temperature before the solvent was removed under reduced pressure to provide compound 2 as a white solid (235 mg, 99%). ^1H NMR (200 MHz, DMSO- d_6) δ 8.59 (s, 1H), 7.85 (d, J = 8.2 Hz, 2H), 7.32 (m, 3H).

Example 149: 6-Phenyl-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide sodium salt
Compound 149 was prepared according to the method described for compound 148; white solid (96%). ^1H NMR (200 MHz, DMSO- d_6) δ 8.65 (s, 1H), 7.93 (d, J =8.8Hz, 2H), 7.70 (d, J =8.8Hz, 2H), 7.36 (m, 2H), 7.24 (s, 1H), 6.90 (d, J =6.4Hz, 1H), 3.81 (s, 3H).

Example 150: 6-Phenyl-imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide sodium salt
Compound 150 was prepared according to the method described for compound 148; white solid (96%). ^1H NMR (200 MHz, DMSO- d_6) δ 8.71 (s, 1H), 7.98 (m, 4H), 7.79 (d, J =8.2Hz, 2H), 7.69 (m, 2H).

Example 151: 6-(4-Azido-2,3,5,6-tetrafluorophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide

2-Bromo-4'-azido-2',3',5',6'-tetrafluoroacetophenone (Keana, J. F. W.; Cai, S. X. *J. Org. Chem.*, 1990, 55, 3640) (353 mg, 1 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide

(148 mg, 1 mmol) were refluxed in ethanol (10 mL) for 60 hours. The resulting solid was filtered, washing twice for cold methanol (2 mL), to provide compound 114 (102 mg, 25 %) as a white powder. ^1H NMR (200MHz, DMSO- d^6) δ 8.81 (t, $J=2.0\text{Hz}$, 1H), 8.79 (br s, 2H).

Example 152: 6-(4-azido-2,3,5,6-pentafluorophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-N,N-dimethylsulfonamide

Compound 152 was preped in a manner similar to compound 138. ^1H NMR (200MHz, DMSO- d^6) δ 8.22 (t, 1H), 3.07 (s, 6H).

Example 153: 6-(4-Nitrophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide
2-Bromo-4'-nitroacetophenone (2.44 g, 10.0 mmol) and 2-amino-1,3,4-thiadiazole-5-sulfonamide (1.50 g, 10.0 mmol) were refluxed in 1,4-dioxane (20 mL) for 48 hrs. The resulting solution was cooled on ice and the resulting precipitate was collected by filtration to provide compound 153 as a white crystalline solid (2.40 g, 67 %). ^1H NMR (200MHz, DMSO- d^6) δ 9.18 (s, 1H), 8.69 (br s, 1H), 8.35 (d, 2H), 8.16 (d, 2H).

Example 154: Protection of SCG neurons from anti-NGF killing
SCG neurons were isolated from day 1 neonatal Sprague Dawley rats, plated at a cell density of 5,000 cells/well, and incubated in Biowhittaker Utraculture containing 1% Penstrep, 1% L-glutamine, 0.7% ARAC, 3% rat serum, and NGF (50 ng/mL, Calomone Labs), at 37 °C, under a 5% CO_2 atmosphere. After 4 days the cells were treated with anti-NGF antibody (Sigma). At this time compound was added and the cells were maintained serum and NGF free for 48 hours, at which time viability was assessed using Alamar Blue (Medicorp) staining.

Table 3a summarizes selected IC(50) values from compounds tested using this protocol.

<p style="text-align: center;">Table 3a</p> <p style="text-align: center;">Rescue from anti-NGF killing of SCG neurons</p>

Compound d	IC(50) (uM)*	Compound	IC(50) (uM)*	Compound	IC(50) (uM)*
1	22	81	5	98	17
2	20	82	25	99	7
3	10	84	>30	106	7
9	8	85	>30	111	7
21	22	86	17	148	22
23	25	87	10	149	7
26	23	88	10	150	7
34	>30	89	10		
35	>30	91	7		
36	17	92	7		
72	17	93	7		
74	20	94	10		
75	10	95	7		
76	5	96	20		
79	7	97	7		
* +/- 1 uM					

Example 155: *In Vitro* Protection of SCG neurons from Taxol killing

SCG neurons were isolated from day 1 neonatal Sprague Dawley rats, plated at a cell density of 10,000 cells/well, and incubated in Biowhittaker Utraculture containing 1% Penstrep, 1% L-glutamine, 0.7% ARAC, 3% rat serum, and NGF (50 ng/mL, Calomone Labs) at 37 °C, under a 5% CO₂ atmosphere. After 5 days the cells were treated with compound and Taxol™ (50 ng/mL). Viability was assessed 48 hours later using MTS (Promega) staining.

Table 3b summarizes selected IC(50) values from compounds tested using this protocol.

Table 3b

Rescue from anti-NGF killing of SCG neurons

Compounds	IC(50) (uM)*	Compound	IC(50) (uM)*	Compound	IC(50) (uM)*
1	7	47	6	81	3
4	5	48	5	82	2
5	5	49	5	87	5

6	3	50	7	95	3
7	4	51	5	99	2
8	5	52	3	101	>30
11	3	53	5	102	>30
12	5	54	10	103	>30
13	7	55	15	104	7
14	5	56	3	105	7
15	10	57	6	107	20
16	5	58	30	108	5
17	3	59	10	109	7
18	20	60	25	110	>30
19	15	61	10	111	2
20	15	62	15	112	5
21	7	63	7	113	7
22	25	64	10	114	7
24	7	65	15	115	7
25	5	66	20	116	7
26	7	67	10	117	3
30	10	68	7	118	17
31	10	70	22	120	7
32	10	71	>30	121	2
37	10	72	10	122	8
38	3	73	2	123	>30
40	23	74	7	124	3
41	3	75	5	125	3
42	3	76	2	128	2
46	7	77	2	129	7
130	2	141	>30	153	5
131	3	142	>30		
132	1	143	10		

134	1	144	15
135	7	145	20
136	5	146	20
137	10	147	17
138	2	148	7
139	10	151	2
140	5	152	2

Figure 1 illustrates the protection provided by compound 1 (referred to here as AEG3482) against Taxol™ induced killing. P1 Sprague Dawley rat SCG neurons were cultured and incubated with NGF (50 ng/mL) for 5 days. Addition of Taxol™ (50 ng/mL) resulted in a 72% loss in viability as measured by MTS staining. Co-treatment with compound 1 resulted in 100% protection at 10 uM, with an IC₅₀ of 7 uM.

Example 156: *In Vitro* Protection of SCG neurons from cisplatin killing
SCG neurons were isolated from day 1 neonatal Sprague Dawley rats, plated at a cell density of 10,000 cells/well, and incubated in Biowhittaker Utraculture containing 1% Penstrep, 1% L-glutamine, 0.7% ARAC, 3% rat serum, and NGF (50 ng/mL, Calomone Labs) at 37 °C, under a 5% CO₂ atmosphere. After 5 days the cells were treated with compound and cisplatin (3 µg/mL). Viability was assessed 48 hours later using MTS (Promega) staining.

Table 4: Protection of SCG neurons against cisplatin killing

<u>Entry</u>	<u>Compound</u>	<u>IC₅₀ (± 1 µM)</u>
1	1	5

Example 157: *In Vitro* Protection of SCG neurons from Vincristine killing
SCG neurons were isolated from day 1 neonatal Sprague Dawley rats, plated at a cell density of 10,000 cells/well, and incubated in Biowhittaker Utraculture containing 1% Penstrep, 1% L-glutamine, 0.7% ARAC, 3% rat serum, and NGF (50 ng/mL, Calomone Labs) at 37 °C, under a 5% CO₂ atmosphere. After 5 days the cells were treated with

compound and vincristine (50 ng/mL). Viability was assessed 48 hours later using MTS (Promega) staining.

Table 5: Protection of SCG neurons against Vincristine killing

<u>Entry</u>	<u>Compound</u>	<u>IC₅₀ (\pm 1 μM)</u>
1	1	10

Example 158: Protection of motor neurons in layer V of the motor cortex
350 μ M slices of P1 rat motor cortex were obtained using a McIlwain tissue chopper (Mickle Laboratory Engineering Co., England). Slices were cultured in 50% Neurobasal, 25% HBSS, 25% Horse serum, 1% penicillin/streptomycin, 2mM glutamine, 6.4mg/mL glucose for 2 weeks. Neuronal death was initiated by addition of 5mM malonate. Test compounds were added coincident with malonate and slices were cultured for an additional two weeks. Slices were fixed in 4% paraformaldehyde and stained with SMI-32 antibody (Stemberger monoclonals, Maryland). Large SMI positive cells with apical dendrites residing in layer V of the the cortex were identified as motor neurons and counted. Malonate treatment greatly reduced the SMI-positive motor neuron count.

Figure 2 illustrates the protection of cortical motor neurons from malonate killing. Slices of P1 rat motor cortex (350 μ M) were treated with malonate and incubated in media for 14 days, before malonate and drug were added. Part (a) shows control motor neurons. Large sized diamond-shaped neurons are visible; part (b) shows malonate treatment alone, which results in killing with a complete loss of neurons; and part (c) shows 90% rescue of cortical motor neurons in the presence of compound 91 (1 μ M) and malonate. In Part C, large diamond-shaped neurons are again visible.

Example 159: Co-treatment of HA460 and OV2008 cell line with Taxol™ and Compound 1

HA460 and OV2008 cells were plated and incubated for 48 hours. Compound 1 and/or compound 1 and Taxol™ were added. Viability was determined after 24 hours, staining with MTT (Promega).

Figure 3 illustrates the co-treatment of H460 and OV 2008 cell lines with Taxol™ and compound 1. HA460 lung carcinoma and OV2008 ovarian carcinoma cells were treated with Taxol™ (50 nM) and/or Taxol™ (50 nM) + compound 1 (noted as AEG 03482) at levels of 5, 10, and 20 uM. Compound 1 did not protect HA460 or OV2008 cells from Taxol™ induced apoptosis.

Example 160: Protection of Sprague Dawley rats from Taxol™ induced neuropathies. Adult Sprague Dawley rats were treated with Taxol™ (IP, 9 mg/kg in Cremophor EL and ethanol) twice weekly for 3 weeks (J. Neuro-Oncology (1999) 41: 107-116). Compound was administered 1 hour prior to Taxol™ treatment (IP, 1, 5 and 10 mg/kg in hydroxypropyl-β-cyclodextrin). Taxol™ treated control animals were treated with saline solution at the same time of Compound treated animals. Non-treated control animals were treated with saline solution as above. Weight gain was measured every second day, starting at Day 1. Gait analysis was measured by quantifying the refracted light captured by a video camera as the animals walked over a glass plate, 2 days after the final Taxol™ treatment (Physiology and Behavior (1994), 55(4): 723-726; Med. Sci. Res. (1988) 16: 901-902). This data was analyzed by Northern Eclipse software. H/M wave recovery was analyzed using standard procedures 2 days after the final Taxol™ treatment (Muscle Nerve (1998) 21: 1405-1413; Annals of Neurology (1998) 43 (1): 46-55).

Figure 4 shows weight loss induced by Taxol™. Male Sprague Dawley rats were treated with 50% HPDC vehicle (veh/veh), compound 1 dissolved in 50% HPDC at 1, 5, or 10 mg/kg (veh/1, veh/5, veh/10, respectively), or Taxol™ (9 mg/kg) + compound 1 dissolved in 50% HPDC at 1, 5, and 10 mg/kg (Tax/1, Tax/5, Tax/10) according to the dosing regime described in Example 123. Weight measurements were made every other day.

Figure 5 shows gait disturbance induced by Taxol™ with compound 1. Two days after the completion of drug treatments animal walking gait was analyzed according to a) total imprint area, and b) total number of contact points. Compound 1 prevented Taxol™ induced gait disturbance.

Figure 6 illustrates the effect of Compound 1 on H-reflex amplitude, a measurement of H/M wave disturbance induced by Taxol™. Two days after the completion of drug treatments, the dorsal root ganglia and attached nerves were dissected bilaterally from L4 and L5 and their H/M wave conductance measured. Compound 1 caused a reversal in H/M wave disturbance induced by Taxol™

Example 161: Sciatic Nerve Crush Injury Model

Male Sprague Dawley rats were anaesthetized (halothane and buprenorphine) and the right hind leg was blunt dissected to expose the sciatic nerve at mid-thigh. The nerve was crushed twice for a total of 30 seconds using No.7 Dumont jeweller's forceps. The incision is sutured and the animals are allowed to recover for 28 days. Functional recovery was measured by gait, nerve conductance and toe spread measurements between digits 1 and 5 and digits 2 and 4.

Figure 7 illustrates sciatic nerve recovery after crush injury, as indicated by inner toe spread. Male Sprague Dawley rats were subjected to sciatic nerve crush and treated with either vehicle control, compound 1 or compound 76 (noted as AEG 33764). Compounds 1 and 76 induced increased recovery in toe spread area.

Example 162: Optical Stroke Model

The right eye of each rat was dilated fully using 1% tropacamide and 2.% pheylephrine hydrochloride (Alcon Canada). A single drop of 0.5% proparacaine (Alcon) was used as a topical anesthetic. The anterior chamber of the right eye was cannulated with a 30-gauge needle connected to a saline reservoir and a manometer to monitor intraocular pressure. Intraocular pressure was raised to 110 mm Hg by raising the saline reservoir for 60 minutes. This increase in pressure collapses the central retinal artery. Retinal ischemia

was confirmed by whitening of the iris and loss of red reflex. After 60 minutes of ischemia, the intraocular pressure was normalized and the needle withdrawn. A 33-gauge blunt needle (Hamilton) was inserted through the corneal puncture, maneuvered around the lens displacing it medially, and advanced into the intravitreal space. A 2 mL volume of drug or vehicle (50% HPCD) was injected into the vitreous of the eye. The needle was withdrawn and maxitrol (Alcon) was applied to the cornea to prevent infection. Alternatively, drug was given subcutaneously before or after the insult, for a period of up to 14 days.

Optical function after 24 hrs, 28 hrs and 7 days was assessed using ERG measurements and histological staining of the DRG layer.

Figure 8 shows protection of DRGs by compound 1 after ocular stroke. Ocular stroke was induced in the right eye of rats resulting in almost complete loss of the DRG population, as seen here by a loss in reactivity of the optic fiber to stimulation. Compound 1 was delivered intravitreally followed by subsequent daily injections for 1 week post-ischemia (post stroke). Compound 1, given post stroke, protects the DRG population allowing for normal conductance.

Example 163: CA II inhibition

CA II inhibition was measured using the protocol described by Pocker, Y.' Stone, *J.Biochemistry* 1967, 6, 668. The IC (50)s of selected compound represented by Formula I are listed in Table 6.

Table 6 : CA II inhibition by compounds represented by formula I

<u>Compounds</u>	<u>IC(50) (uM)</u>	<u>Compound</u>	<u>IC(50) (uM)</u>	<u>Compound</u>	<u>IC(50) (uM)</u>
1	0.250	21	5.32	49	0.466
4	0.217	22	0.153	50	0.938
5	0.192	24	0.613	72	1.61
6	0.164	25	0.302	72	2.19

7	0.581	37	0.199	74	1.68
8	1.47	38	0.577	75	0.441
11	1.80	39	0.154	76	0.526
12	1.59	40	1.52	81	1.58
13	4.05	41	0.346	82	5.43
14	0.198	42	0.272	87	0.128
15	0.152	43	0.886	99	0.914
16	0.150	44	0.619	105	0.150
17	0.179	45	0.166	111	53.2
18	0.337	46	0.601	137	2.06
19	0.373	47	0.361	139	11.3
20	0.404	48	0.288	142	60.3

Example 164: Neuroprotection of Cortical Neurons in the Presence of B-Amyloid

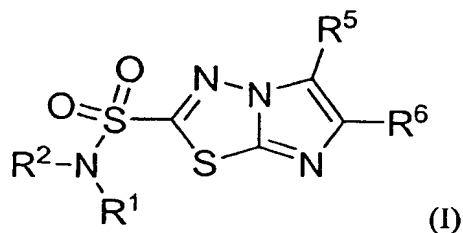
Primary neuronal/glial cortical cultures were established from postnatal day 1 Sprague Dawley rats. Cerebral cortices were isolated and dissociated with 0.25% trypsin for 20 minutes at 37 degrees. The tissue was then triturated in PBS containing 0.1% bovine serum albumin and 0.2mg/ml DNase. Cells were plated in poly D-lysine coated 96 well plates at a density of 1e6 cells per mL. Cultures were maintained at 37 degrees in 5% CO2/95% air for 2 weeks in Neurobasal (Gibco) supplemented with B27, glutamine, and penicillin/streptomycin. 5ng/mL AraC was added after 48 hours. After 2 weeks cells were exposed to 10 uM 25-35 amyloid beta peptide with and without 10 uM AEG33764. After 2 days of treatment apoptotic cells were detected with Cy3-conjugated annexin V (Sigma).

Figure 9 shows the protection of provided by Compound 76 from amyloid beta 25-35 toxicity. Mixed neuronal/cortical cultures were obtained from P1 rat cortex. After 2 weeks in vitro cells were exposed to 10 uM 25-35 amyloid beta peptide. Top (a) shows control untreated cultures display low level annexin V staining. Middle (b) shows 48 hour treatment with amyloid beta peptide results in the appearance of apoptotic cells which

stain with annexin V on the cell periphery. Bottom (c) illustrates co-treatment with 10 μ M Compound 76 prevents the occurrence of annexin V stained cells.

CLAIMS

1. The use of imidazo[2,1-*b*]thiadiazole sulfone analogues and precursors of the present invention include compounds of the Formula I:

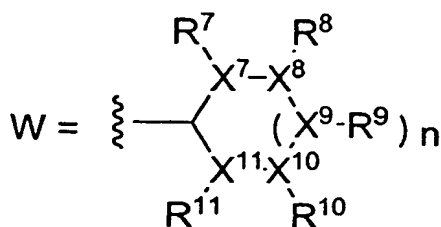


or pharmaceutically acceptable salts thereof wherein:

R^1 and R^2 are independently selected from the group consisting of H, lower alkyl, substituted lower alkyl, and fluoroalkyl;

R^5 is selected from the group consisting of H, halogen, cyano, azide, thiocyanate, formyl, lower alkyl, substituted lower alkyl, fluoroalkyl, aralkyl, substituted aralkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

R^6 is selected from the group consisting of H, lower alkyl, substituted lower alkyl, fluoroalkyl, substituted fluoroalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, adamantly, coumarinyl, and substituted coumarinyl; or R^6 is represented by W:



wherein:

n represents 0 or 1;

the ring system containing X^7-X^{11} represents a 5 or 6 membered aromatic or heteroaromatic ring system, in which X^7-X^{11} are independently selected from the group consisting of C, N, S, and O;

when any one of X^7-X^{11} independently represents C, a respective R^7-R^{11} is independently selected from the group consisting of:

- a) H, halogen, nitro, cyano, lower alkyl, substituted lower alkyl, fluoroalkyl, aralkyl, substituted aralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, acyl, lower alkylcarbonyl, substituted lower alkylcarbonyl, arylcarbonyl, substituted arylcarbonyl, heteroarylcarbonyl, or substituted heteroarylcarbonyl;
- b) $SO_2NR^{16}R^{17}$ wherein R^{16} and R^{17} are independently selected from the group consisting of lower alkyl, substituted lower alkyl, aralkyl, substituted aralkyl, heteroaralkyl, substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl; or wherein R^{16} and R^{17} are joined to form an alkyl, substituted alkyl, heteroalkyl, or substituted heteroalkyl ring system;
- c) SO_nR^{18} wherein $n=0, 1$ or 2 , and wherein R^{18} is selected from the group consisting of lower alkyl, substituted lower alkyl, aralkyl, substituted aralkyl, heteroaralkyl, substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;
- d) XR^{19} wherein X is defined as S or O, and R^{19} is defined as alkyl, substituted alkyl, fluoroalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, acyl, lower alkylcarbonyl, substituted lower alkylcarbonyl, arylcarbonyl, substituted arylcarbonyl, heteroarylcarbonyl, substituted heteroarylcarbonyl, lower alkylaminocarbonyl, arylaminocarbonyl, or substituted arylaminocarbonyl;
- e) $NR^{14}R^{15}$ wherein R^{14} and R^{15} are defined as lower alkyl joined to form an alkyl, substituted alkyl, heteroalkyl, or substituted heteroalkyl ring system; and
- f) CO_2R^{20} wherein R^{20} is defined as H, lower alkyl, substituted lower alkyl, aralkyl, substituted aralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, or $NR^{21}R^{22}$, wherein R^{21} and R^{22} are independently selected from the group consisting of lower alkyl, aralkyl, aryl;

wherein when any one of X^7-X^{11} represents N, that nitrogen is attached to the adjacent atoms by either one single and one double bond, or by two single bonds;

wherein when any one of X^7-X^{11} represents N, and that nitrogen is attached to the adjacent atoms by one single and one double bond, the respective R^7-R^{11} represents a lone pair;

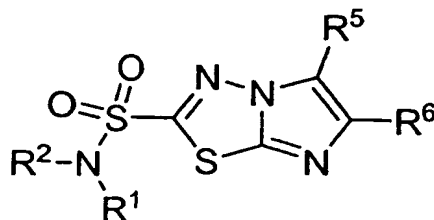
when any one of X^1-X^5 represents N, and that nitrogen is attached to the adjacent atoms by two single bonds, the respective R^7-R^{11} is selected from the group consisting of H, lower alkyl, substituted lower alkyl, aralkyl, substituted aralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, SO_2R^{18} , wherein R^{18} is defined as in c), and COR^{18} , wherein R^{18} is defined as in c);

when $n=0$, R^7 and R^8 , or R^8 and R^9 are combined to form a fused 5, 6, or 7 membered alkyl, substituted alkyl, heteroalkyl, substituted heteroalkyl, heteroaralkyl, substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, or heteroaryl ring system;

when $n=1$ and X^9 represents C, R^7 and R^8 , or R^8 and R^{10} are combined to form a fused 5, 6, or 7 membered alkyl, substituted alkyl, heteroalkyl, substituted heteroalkyl, aryl, substituted aryl, or heteroaryl ring system; and

any one of R^7-R^{11} represents a lone pair when a respective X^7-X^{11} represents S or O.

2. The imidazo[2,1-*b*]thiadiazole sulfonamide derivatives and precursors according to Formula I:



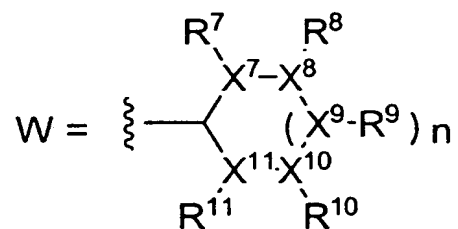
(I)

or pharmaceutically acceptable salts thereof wherein:

R^1 and R^2 are individually selected from the group consisting of H, lower alkyl, substituted lower alkyl, and fluoroalkyl;

R^5 is selected from the group consisting of H, halogen, cyano, azide, thiocyanate, formyl, lower alkyl, substituted lower alkyl, fluoroalkyl, aralkyl, substituted aralkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

R^6 is selected from the group consisting of H, lower alkyl, substituted lower alkyl, fluoroalkyl, substituted fluoroalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, adamantly, coumarinyl, and substituted coumarinyl; or R^6 is represented by W:



wherein:

n represents 0 or 1;

the ring system containing X^7-X^{11} represents a 5 or 6 membered aromatic or heteroaromatic ring system, in which X^7-X^{11} are independently selected from the group consisting of C, N, S, and O;

when any one of X^7-X^{11} independently represents C, a respective R^7-R^{11} is independently selected from the group consisting of:

- a) H, halogen, nitro, cyano, lower alkyl, substituted lower alkyl, fluoroalkyl, aralkyl, substituted aralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, acyl, lower alkylcarbonyl, substituted lower alkylcarbonyl, arylcarbonyl, substituted arylcarbonyl, heteroarylcarbonyl, or substituted heteroarylcarbonyl;
- b) $SO_2NR^{16}R^{17}$ wherein R^{16} and R^{17} are independently selected from the group consisting of lower alkyl, substituted lower alkyl, aralkyl, substituted aralkyl,

- heteroaralkyl, substituted heteroaralkyl aryl, substituted aryl, heteroaryl, and substituted heteroaryl, or wherein R^{16} and R^{17} are joined to form an alkyl, substituted alkyl, heteroalkyl, or substituted heteroalkyl ring system;
- c) SO_nR^{18} wherein $n=0, 1$ or 2 , and wherein R^{18} is selected from the group consisting of lower alkyl, substituted lower alkyl, aralkyl, substituted aralkyl, heteroaralkyl, substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl;
- d) XR^{19} wherein X is defined as S or O , and R^{19} is defined as alkyl, substituted alkyl, fluoroalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, acyl, lower alkylcarbonyl, substituted lower alkylcarbonyl, arylcarbonyl, substituted arylcarbonyl, heteroarylcarbonyl, substituted heteroarylcarbonyl, lower alkylaminocarbonyl, arylaminocarbonyl, or substituted arylaminocarbonyl;
- e) $NR^{14}R^{15}$ wherein R^{14} and R^{15} are defined as lower alkyl joined to form an alkyl, substituted alkyl, heteroalkyl, or substituted heteroalkyl ring system; and
- g) CO_2R^{20} wherein R^{20} is defined as H , lower alkyl, substituted lower alkyl, aralkyl, substituted aralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, or $NR^{21}R^{22}$, wherein R^{21} and R^{22} are independently selected from the group consisting of lower alkyl, aralkyl, aryl;

wherein when any one of X^7-X^{11} represents N , that nitrogen is attached to the adjacent atoms by either one single and one double bond, or by two single bonds;

wherein when any one of X^7-X^{11} represents N , and that nitrogen is attached to the adjacent atoms by one single and one double bond, the respective R^7-R^{11} represents a lone pair;

when any one of X^1-X^5 represents N , and that nitrogen is attached to the adjacent atoms by two single bonds, the respective R^7-R^{11} is selected from the group consisting of H , lower alkyl, substituted lower alkyl, aralkyl, substituted aralkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, SO_2R^{18} , wherein R^{18} is defined as in c), COR^{18} , wherein R^{18} is defined as in c);

when $n=0$, R^7 and R^8 , or R^8 and R^9 are combined to form a fused 5,6, or 7 membered alkyl, substituted alkyl, heteroalkyl, substituted heteroalkyl, heteroaralkyl, substituted heteroaralkyl, aryl, substituted aryl, heteroaryl, or heteroaryl ring system;

when $n=1$ and X^9 represents C, R^7 and R^8 , or R^8 and R^{10} are combined to form a fused 5, 6, or 7 membered alkyl, substituted alkyl, heteroalkyl, substituted heteroalkyl, aryl, substituted aryl, or heteroaryl ring system; and

any one of R^7 - R^{11} represents a lone pair when the respective X^7 - X^{11} represents S or O;

with the proviso that compounds 1, 4, 10, 14, 20, 60, 72, 105, 109, 111, 114, 124, 126, 127, 133, and 153 are excluded.

3. An imidazo[2,1-*b*]-1,3,4-thiadiazole-2-sulfonamide derivatives selected from the group consisting of compound 2, 3, 5, 6, 7, 8, 9, 11, 12, 13, 15, 16, 18, 19, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 61, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 106, 107, 108, 110, 113, 115, 116, 117, 118, 119, 120, 121, 122, 123, 125, 129, 130, 131, 132, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, and 152.
4. Use of a compound according to any one of claims 2 or 3 for the prevention or treatment of condition selected from the group consisting of neurodegenerative diseases of both the central and peripheral nervous systems, or in combination with other compounds known to the art, for the treatment of the above disease states.
5. Treatment or prevention of a condition selected from the group consisting of neurodegenerative diseases of both the central and peripheral nervous systems, by

administration of an effective amount of a compound according to claim 2 or 3 to a patient in need thereof.

6. Use of a compound according to claim 2 or 3 for the treatment of degenerative diseases of the eye.
7. Treatment or prevention of a condition selected from the group consisting of degenerative diseases of the eye, by administration of an effective amount of the compound according to claim 2 or 3 to a patient in need thereof.
8. Use of a compound according to claim 2 or 3 for induction of axonal growth and repair for the prevention or treatment of neurodegenerative diseases of both the central and peripheral nervous systems, or in combination with other compounds known to the art, for the treatment of the above disease states
9. Treatment or prevention of a condition resulting from loss of axonal growth and repair, by administration of an effective amount of the compound according to claim 2 or 3 to a patient in need thereof.
10. Use of a compound according to claim 2 or 3 for altering signal transduction.
11. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound according to claim 2 or 3 in combination with a pharmaceutically acceptable carrier.
12. A pharmaceutical package comprising the pharmaceutical composition according to claim 11 in combination with directions for use.

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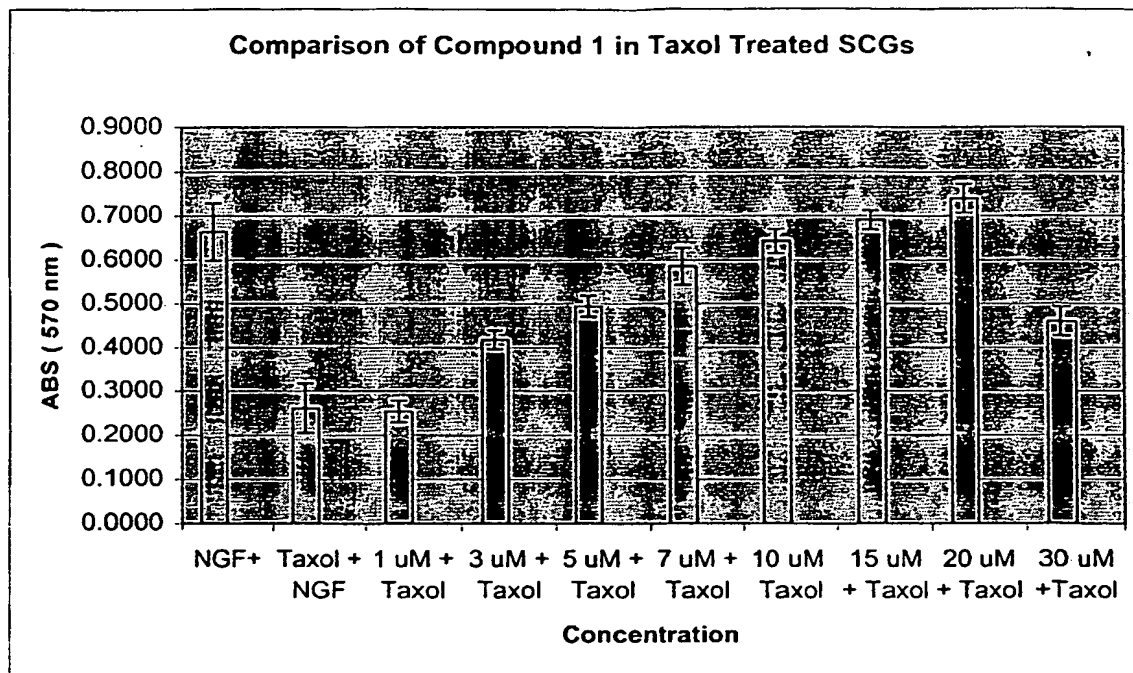
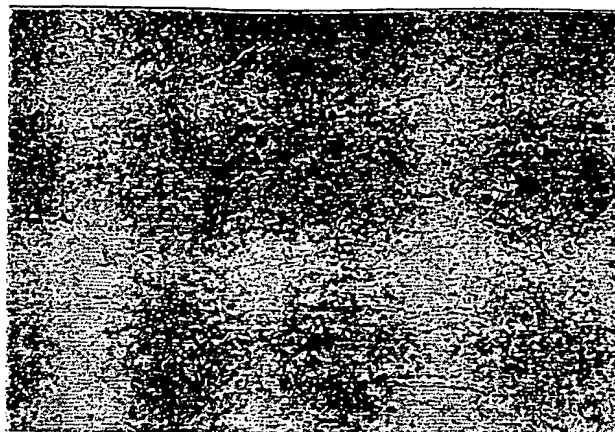


FIG. 1

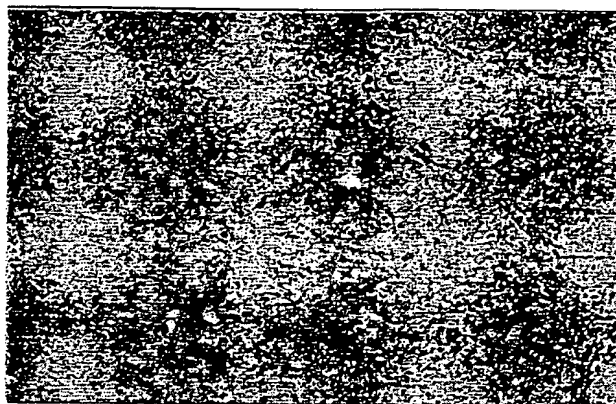
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a)



b)



c)

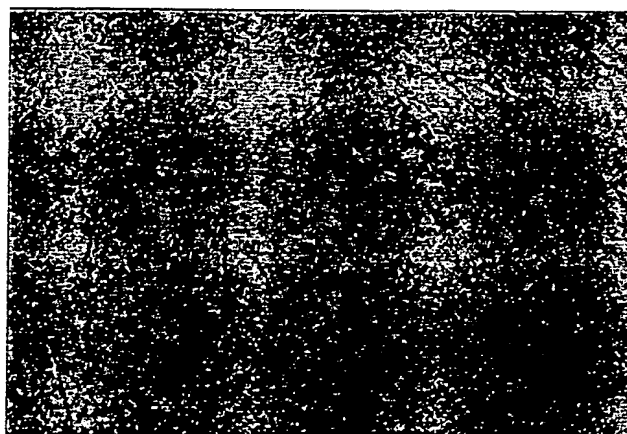
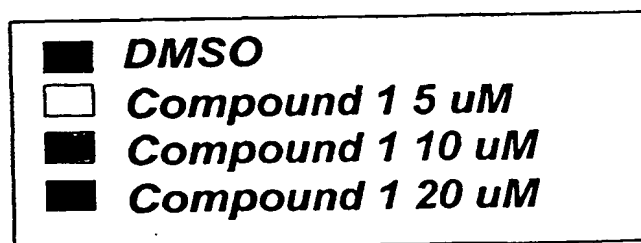
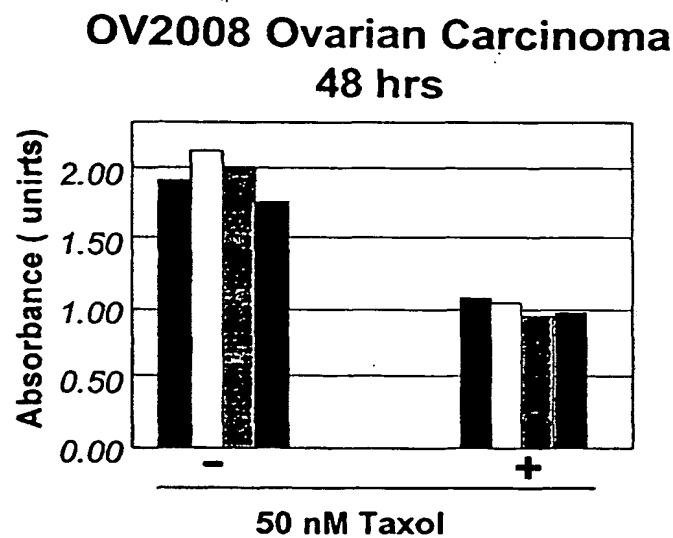
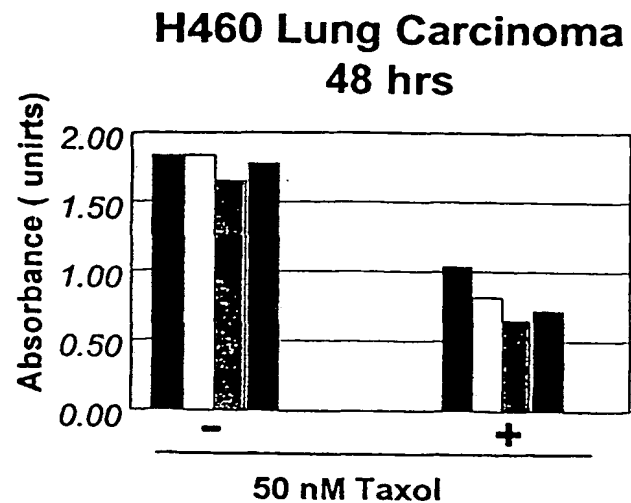


FIG. 2

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**FIG. 3****BEST AVAILABLE COPY**

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Weight loss induced by Taxol (Compound 1)

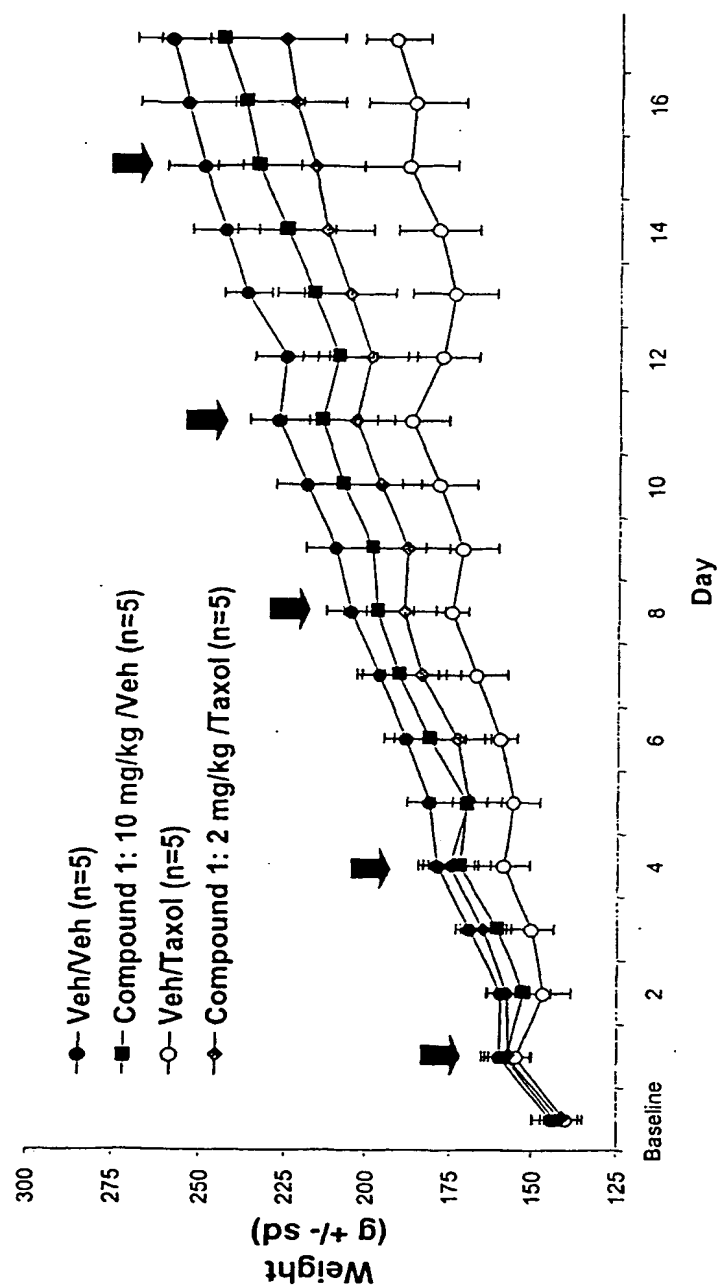


FIG. 4

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Effect of Compound 1 and Taxol on Number of Paw Contact Points

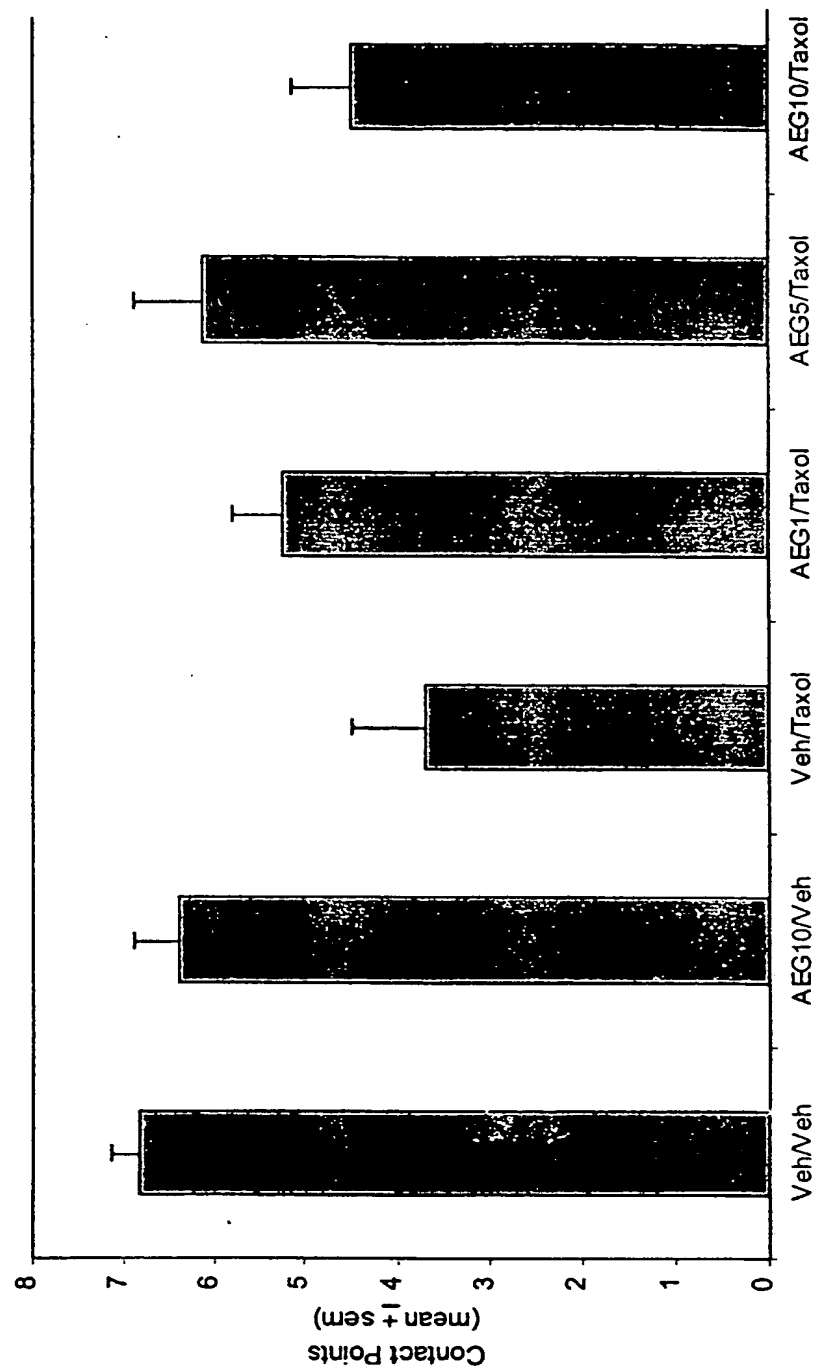


FIG. 5

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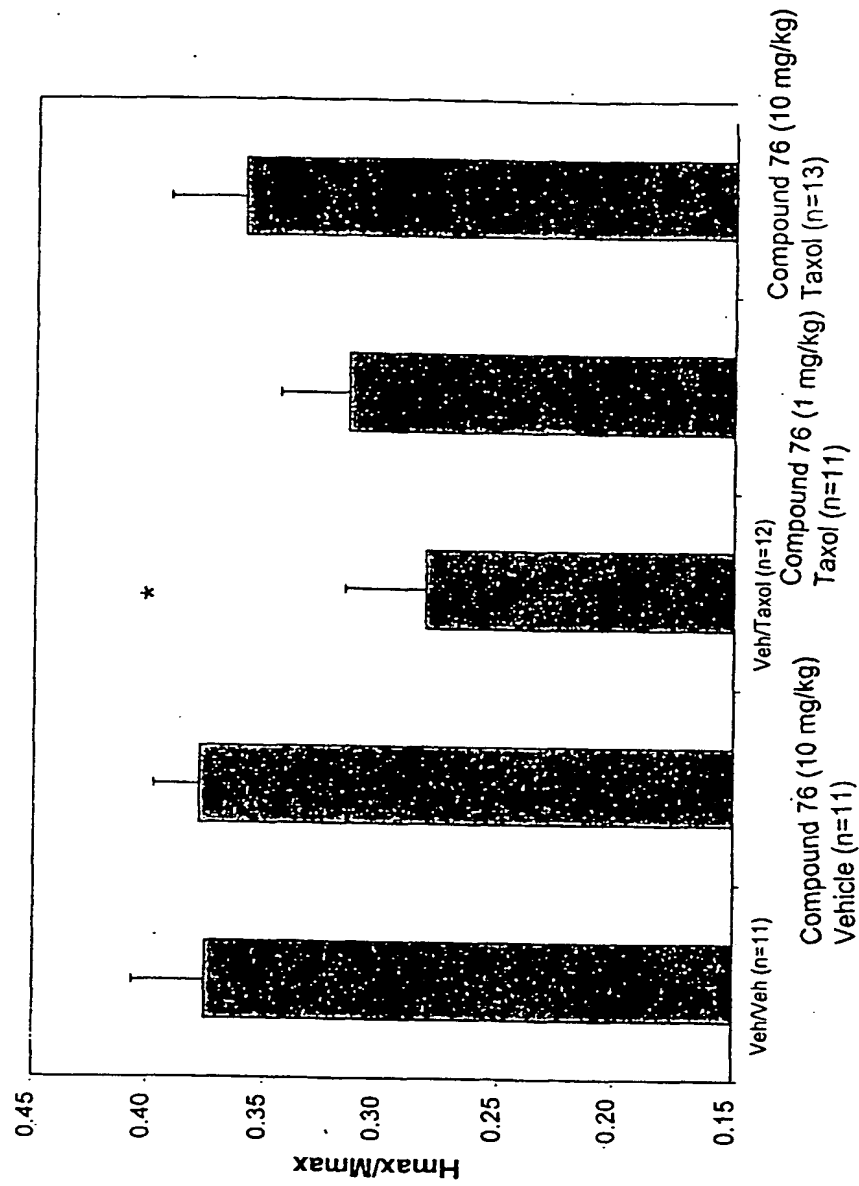


FIG. 6

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Inner Toe Spread Over Days

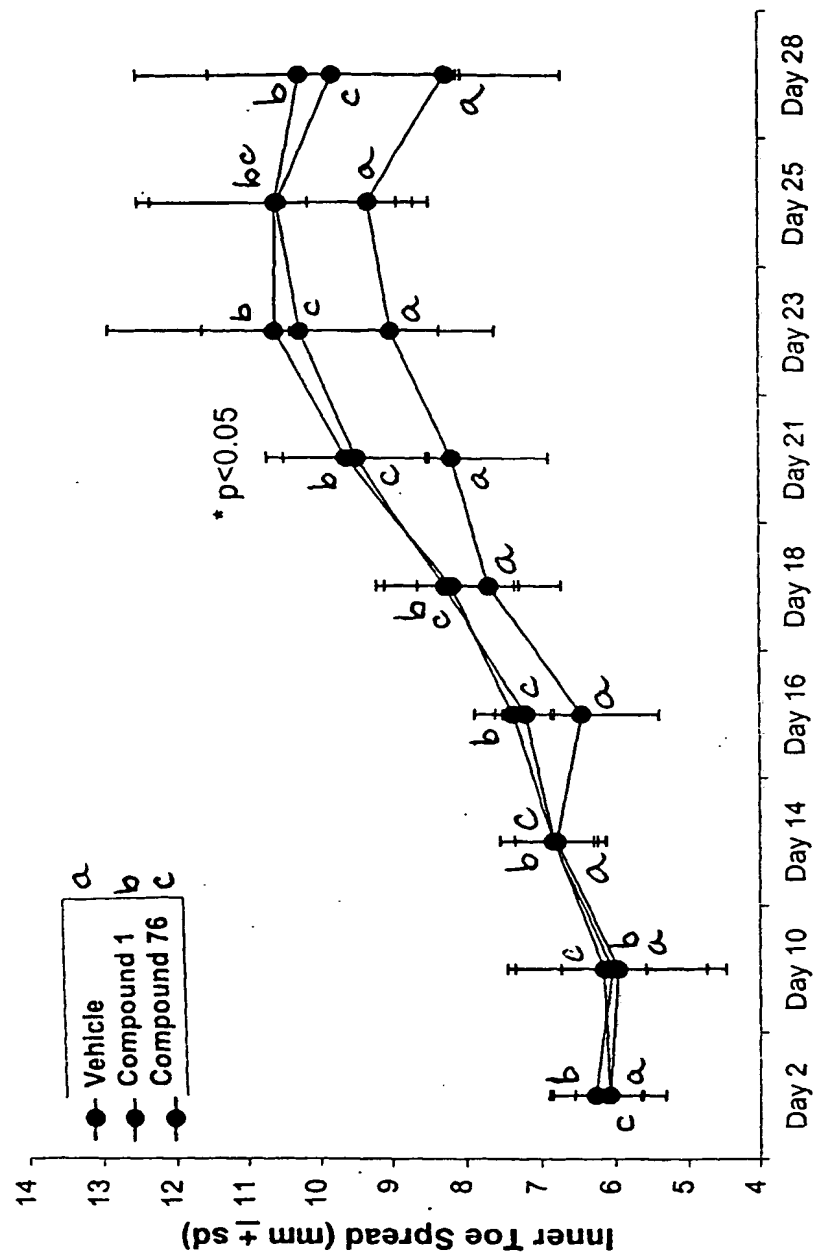


FIG. 7

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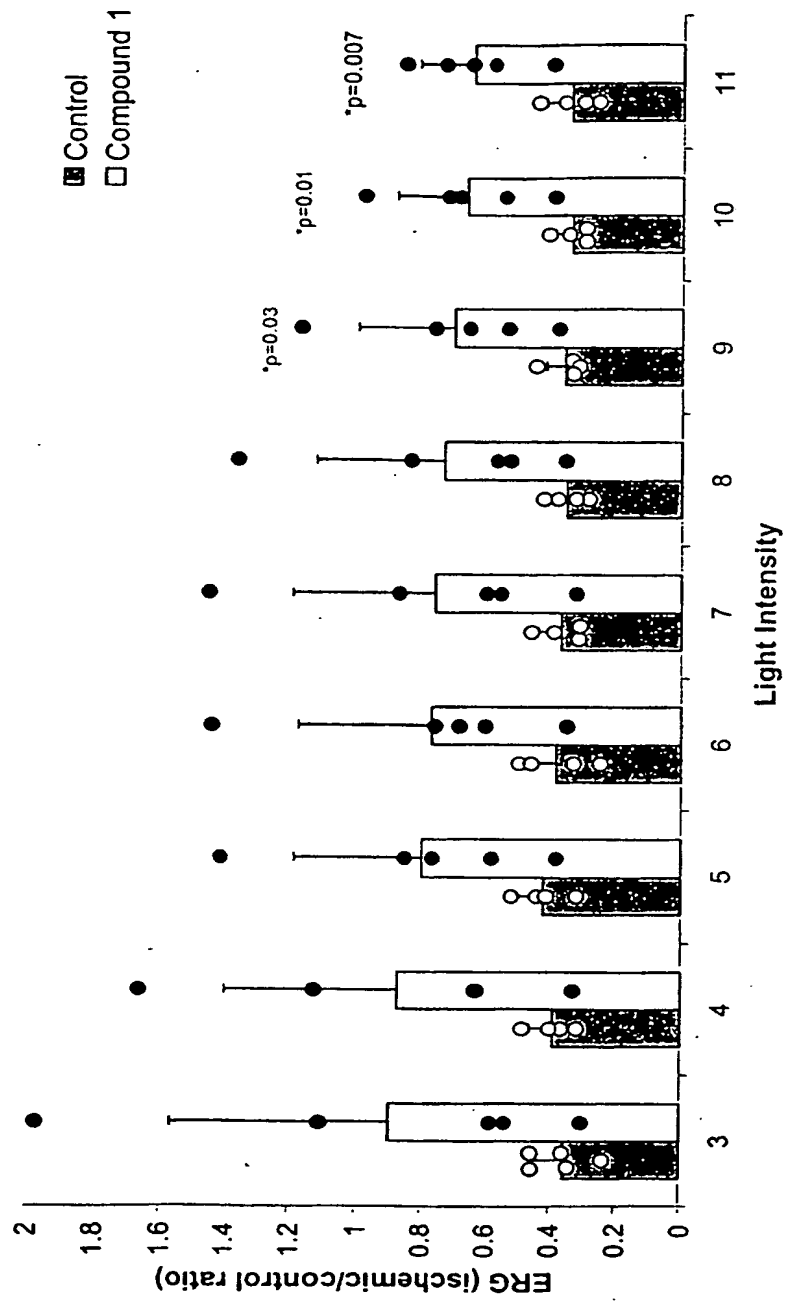


FIG. 8

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a)



b)



c)

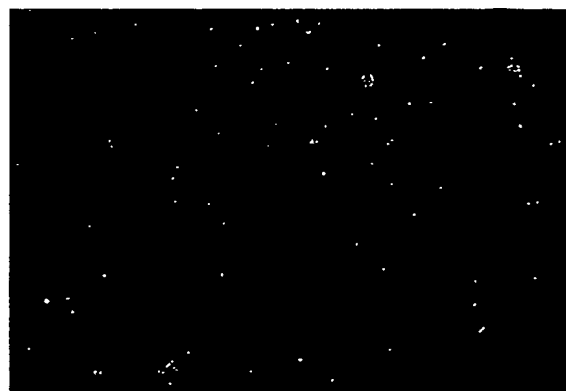


FIG. 9

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D513/04 A61K31/41 A61P25/00 //(C07D513/04,285:00,
235:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>SUPURAN CT ET AL: "Complexes with biologically active ligands. Part 10 inhibition of carbonic anhydrase isozymes I and II with metal complexes of imidazo[2,1-b]-1,3,4-thiadiazole-2-sulfonamide"</p> <p>METAL-BASED DRUGS, vol. 4, no. 1, 1997, pages 19-26, XP002232873 page 19, paragraph FINAL -page 20, paragraph 2; examples 7,8</p> <p style="text-align: center;">--- -/--</p>	1,2,4-7



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

21 March 2003

Date of mailing of the international search report

08/04/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Bakboord, J

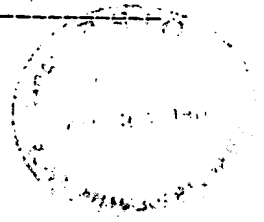
C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>BARNISH IT ET AL: "Cerebrovasodilatation through selective inhibition of the enzyme carbonic anhydrase. 2. imidazo[2,1-b]thiadiazole and imidazo[2,1-b]thiazolesulfonamides" JOURNAL OF MEDICINAL CHEMISTRY, vol. 23, 1980, pages 117-121, XP002232874 USA cited in the application examples 2,5-11,13-20; table 1</p>	1,2,4,5
X	<p>SULTANPUR CM ET AL: "Synthesis, anticonvulsant and analgesic activities of some 6-substituted imidazo[2,1-b]-1,3,4-thiadiazole-2-sulfonamides and their 5-bromo derivatives" ARZNEIMITTEL-FORSCHUNG, vol. 46, no. 10, 1996, pages 949-952, XP002232875 examples 12-20,22; tables 2,4</p>	1,2,4,5
X	<p>GB 1 464 259 A (PFIZER LTD) 9 February 1977 (1977-02-09) cited in the application page 1, line 7 - line 14; table II</p>	1,2,4,5, 11
X	<p>CONROY CW ET AL: "The nonenzymatic displacement of the sulfamoyl group from different classes of aromatic compounds by glutathione and cysteine" DRUG METABOLISM AND DISPOSITION, vol. 12, 1984, pages 614-618, XP009006657 USA example XIX; table 1</p>	1,2
X	<p>GADAD, ANDANAPPA K. ET AL: "Synthesis and antibacterial activity of some 5-guanylhydrazone/thiocyanat 6-arylimidazo[2,1-b]-1,3,4-thiadiazole-2-sulfonamide derivatives" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY (2000), 35(9), 853-857 , XP004331218 cited in the application examples 3A-3F</p>	1

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>GADAD, ANDANAPPA K. ET AL: "Synthesis and biological evaluation of 5-formyl-6-aryl-imidazo(2,1-b)-1,3,4-thiadiazole-2-N-(dimethylaminomethino)sulfonamides as antitumor agents"</p> <p>ARZNEIMITTEL-FORSCHUNG (1999), 49(10), 858-863 ,</p> <p>XP002232876</p> <p>cited in the application</p> <p>Scheme 1</p> <p>table 2</p>	1
A	<p>-----</p> <p>SUPURAN CT: "Metal complexes of 1,3,4-thiadiazole-2,5-disulfonamide are strong dual carbonic anhydrase inhibitors, although the ligand possesses very weak such properties"</p> <p>METAL-BASED DRUGS,</p> <p>vol. 2, no. 6, 1995, pages 331-336,</p> <p>XP002232877</p> <p>cited in the application</p> <p>examples 5-14; table III</p> <p>-----</p>	1,4

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 1464259	A	09-02-1977	NONE



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